PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07C 279/12, 233/78, 237/24, C07D 215/12, 307/46, 333/26, 213/54, 213/24, A61K 51/00, 49/00, 31/155, 31/165, 31/33

A1

(11) International Publication Number: **WO 99/67203**

(43) International Publication Date: 29 December 1999 (29.12.99)

(21) International Application Number: PCT/SE99/01074

(22) International Filing Date: 16 June 1999 (16.06.99)

(30) Priority Data:
9802206–4 22 June 1998 (22.06.98) SE

(71) Applicant *(for all designated States except MG US)*: ASTRA PHARMA INC. [CA/CA]; 1004 Middlegate Road, Mississauga, Ontario L4Y 1M4 (CA).

(71) Applicant *(for MG only)*: ASTRA AKTIEBOLAG [SE/SE]; S–151 85 Södertälje (SE).

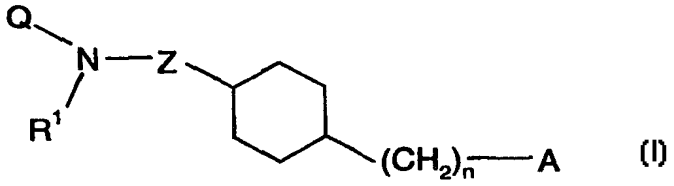
(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: DELORME, Daniel [CA/CA]; MethylGene Inc., 7220 Frederick–Banting, Montreal, Quebec H4S 2A1 (CA). GREGOR, Vlad [US/US]; Alanex Corp., 3550 General Atomics Court, San Diego, CA 92121 (US). ROBERTS, Edward [GB/CA]; Astra Research Centre Montreal, 7171 Fredrick–Banting, St Laurent, Quebec H4S 1Z9 (CA). SUN, Eric [US/US]; Alanex Corp., 3550 General Atomics Court, San Diego, CA 92121 (US).

(74) Agent: ASTRA AKTIEBOLAG; Intellectual Property, Patents, S–151 85 Södertälje (SE).

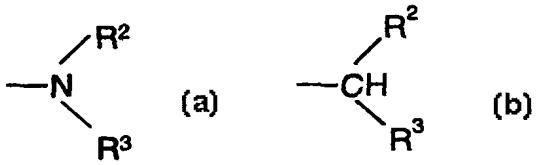
(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: NOVEL COMPOUNDS USEFUL IN PAIN MANAGEMENT



(I)



(57) Abstract

Compounds of general formula (I) wherein A is (a) or (b); Z is $(CH_2)_m$ or a carbonyl group are disclosed and claimed in the present application, as well as their pharmaceutically acceptable salts, pharmaceutical compositions comprising the novel compounds and their use in therapy, in particular in the management of pain. Also intermediates to the compounds of formula (I) are claimed.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

NOVEL COMPOUNDS USEFUL IN PAIN MANAGEMENT

Field of the invention

The present invention is related to novel compounds, to a process for their preparation, intermediates, their use and pharmaceutical compositions comprising the novel compounds. The novel compounds are useful in therapy, and in particular for the treatment of pain.

Background and prior art

The δ receptor has been identified as having a role in many bodily functions such as circulatory and pain systems. Ligands for the δ receptor may therefore find potential use as analgesics, and/or as antihypertensive agents. Ligands for the δ receptor have also been shown to possess immunomodulatory activities.

The identification of at least three different populations of opioid receptors (μ, δ and κ) is now well established and all three are apparent in both central and peripheral nervous systems of many species including man. Analgesia has been observed in various animal models when one or more of these receptors has been activated.

With few exceptions, currently available selective opioid δ ligands are peptidic in nature and are unsuitable for administration by systemic routes. Some non-peptidic δ antagonists have been available for some time (see Takemori and Portoghese, 1992, Ann. Rev. Pharmacol. Tox., 32: 239-269. for review). These compounds, e.g. naltrindole, suffer from rather poor (i.e., < 10-fold) selectivity for the δ receptor vs. μ receptor binding and exhibit no analgesic activity, a fact which underscores the need for the development of highly selective non-peptidic δ ligands.

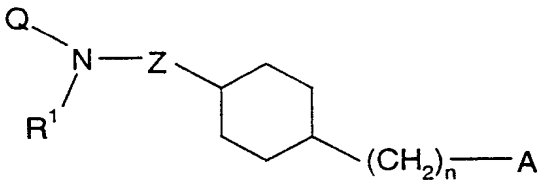
Thus, the problem underlying the present invention was to find new analgesics having improved analgesic effects, but also with an improved side-effect profile over current μ agonists and potential oral efficacy.

Analgesics that have been identified and are existing in the prior art have many disadvantages in that they suffer from poor pharmacokinetics and are not analgesic when administered by systemic routes. Also, it has been documented that preferred compounds, described within the prior art, show significant convulsive effects when administered systemically.

The problem mentioned above has now been solved by developing novel 1,4-substituted cyclohexyl compounds, as will be described below.

Outline of the invention

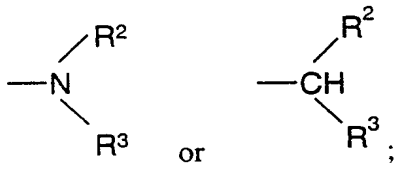
The novel compounds according to the present invention are defined by the formula I



I

wherein

A is



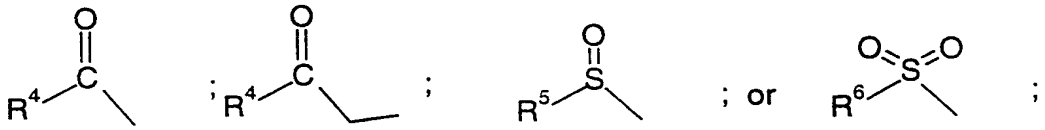
wherein R^2 and R^3 are as defined below;

Z is $(CH_2)_m$ or a carbonyl group;

m and n are each and independently an integer of from 0-3, and one or more of the hydrogens in such an alkylene-chain may optionally be substituted by anyone of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, or hydroxy; *or*
one or more of the methylene groups may optionally be substituted by a heteroatom such as O, N or S;

m and n may not both be 0;

Q is selected from any of CH_3;



wherein

R^4, R^5 and R^6 is each and independently selected from any of

(i) C_6-C_{10} aryl; or

(ii) heteroaryl having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; and

wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined below;

(iii) hydrogen;

(iv) a straight or branched C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl;

(v) C_1-C_3 alkoxy;

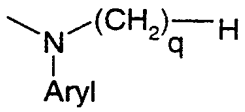
(vi) saturated or unsaturated C_3 - C_{10} cycloalkyl, optionally and independently substituted by one or more aryl groups or heteroaryl groups having from 5 to 10 atoms with the heteroatom(s) being selected from any of S, N and O and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined below;

(vii) -[$(CH_2)_q$-aryl] where q is an integer of from 1-3, and the aryl may optionally be substituted by 1 or 2 substituents Y, where each Y is as defined below;

(viii) -[$(CH_2)_r$-heteroaryl] where r is an integer of from 1-3, the heteroaryl having from 5 to 10 atoms with heteroatoms(s) being selected from any of S, N, and O, optionally and independently substituted by 1 or 2 substituents Y as defined below;

(ix) -[CH_2-O-aryl] where the aryl may optionally be substituted by 1 or 2 substituents Y, where each Y is as defined below;

(x)



where q is an integer of from 1-3, and the aryl is as defined below, optionally substituted by 1 or 2 substituents Y, where each Y is as defined below;

R^1 is selected from anyone of

(i) a straight or branched C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, where each alkyl, alkenyl or alkynyl may optionally be substituted by one or more aromatic or heteroaromatic substituents;

(ii) C_3-C_7 cycloalkyl, optionally comprising one or more unsaturations and optionally substituted by one or more of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, hydroxy; or substituted by one or more aryl(s), or heteroaryl(s) having from 5 to 10 atoms and the heteroatom(s) being selected from any of S, N and O and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents **Y** wherein each Y is as defined below;

(iii) hydrogen, halogen or C_1-C_6 alkoxy;

(iv) C_6-C_{10} aryl;

(v) heteroaryl having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined below;

(vi) 9,10-dihydro-9,10-ethanoantracenyl;

(vii) -[$(CH_2)_q$-aryl] where q is an integer of from 1-3 and the aryl may optionally be substituted by 1 or 2 substituents Y, where each Y is as defined below;

(viii) -[$(CH_2)_r$-heteroaryl] where r is an integer of from 1-3, the heteroaryl having from 5 to 10 atoms and the heteroatoms(s) being selected from any of S, N, and O, and wherein the heteroatom(s) may optionally and independently be substituted by 1 or 2 substituents Y, where each Y is as defined below;

(ix) -[$(CH_2)_q$-aryl-O-$(CH_2)_r$-aryl] where q and r is each and independently an integer of from 1-3;

(x) -$(CH_2)_q$-[C_3-C_6 cycloalkyl] where q is from 1-2, optionally substituted by 1 or 2 substituents Y and wherein Y is as defined below;

R^2 is selected from any of

(i) hydrogen;

(ii) a straight or branched C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, where each alkyl, alkenyl or alkynyl may optionally be substituted by one or more aromatic or heteroaromatic substituents;

(iii) C_6 - C_{10} arylalkyl, wherein the aryl may optionally be substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined below;

(iv) heteoaryl-(C_5 - C_{10} alkyl), where the heteroaryl has from 5 to 10 atoms and the heteroatom being selected from any of S, N and O, and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined below;

(v) C_3-C_{10} cycloalkyl, optionally comprising one or more unsaturations and optionally susbtituted by one or more heteroaryl(s) where the heteroaryl has from 5 to 10 atoms and the heteroatom being selected from any of S, N and O;
and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined below;

(vi) C_6-C_{10} aryl, optionally and independently substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom(s) being selected from any of S, N and O and wherein the heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined below;

(vii) heteroaryl having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined below;

R^3 is selected from anyone of

(i) hydrogen;

(ii) a straight or branched C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, where each alkyl, alkenyl or alkynyl may optionally be substituted by one or more aromatic or heteroaromatic substituents;

(iii) C_6 - C_{10} arylalkyl, wherein the aryl may optionally be substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined below;

(iv) heteoaryl-(C_5 - C_{10} alkyl), where the heteroaryl has from 5 to 10 atoms and the heteroatom being selected from any of S, N and O, and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined below;

(v) C_3-C_{10} cycloalkyl, optionally comprising one or more unsaturations and optionally substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O, and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined below;

(vi)

;

wherein

R^7, R^8, R^9, R^{10} and R^{11} is each and independently selected from

(a) hydrogen;

(b) a straight or branched C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, where each alkyl, alkenyl or alkynyl may optionally be substituted by one or more aromatic or heteroaromatic substituents;

(c) C_6 - C_{10} arylalkyl, wherein the aryl may optionally be substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined below;

(d) heteoaryl-(C_5 - C_{10} alkyl), where the heteroaryl has from 5 to 10 atoms and the heteroatom being selected from any of S, N and O, and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined below;

(e) C_3-C_{10} cycloalkyl, optionally comprising one or more unsaturations and optionally susbtituted by one or more heteroaryl(s) where the heteroaryl has from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined below;

(f) C_6-C_{10} aryl, optionally and independently substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom(s) being selected from any of S, N and O and wherein the heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined below;

or

R^2 and R^3 may optionally form a heterocyclic ring;

Y is each and independently selected from any of hydrogen, CH_3; —$(CH_2)_{p1}CF_3$; halogen; C_1-C_3 alkoxy; hydroxy; -NO_2; -OCF_3; —$CONR^aR^b$; —$COOR^a$; —COR^a; —$(CH_2)_{p2}NR^aR^b$; —$(CH_2)_{p3}CH_3$, $(CH_2)_{p4}SOR^aR^b$; —$(CH_2)_{p5}SO_2R^a$; —$(CH_2)_{p6}SO_2NR^a$; C_4-C_8(alkyl-cycloalkyl) wherein alkyl is C_1-C_2 alkyl and cycloalkyl is C_3-C_6 cycloalkyl; 1 or 2 heteroaryl(s) having from 5 to 10 atoms and the heteroatom(s) being selected from any of S, N and O; and oxides such as N-oxides or sulfoxides; and wherein

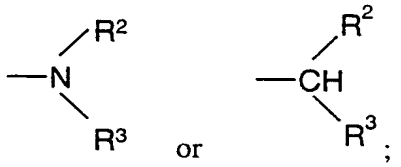
R^a and R^b is each and independently selected from hydrogen, a branched or straight C_1-C_6 alkyl, C_1-C_6 alkenyl, C_3-C_8 cycloalkyl; and wherein

p1, p2, p3, p4, p5 and p6 is each and independently 0, 1 or 2.

Within the scope of the invention are also pharmaceutically acceptable salts of the compounds of the formula (I), as well as isomers, hydrates, isoforms and prodrugs thereof.

Preferred compounds according to the invention are compounds of the formula (I) wherein

A is

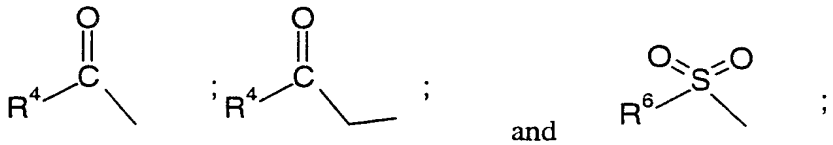


wherein R^2 and R^3 are as defined below;

Z is $(CH_2)_m$ or a carbonyl group;

m and n are each and independently an integer of from 1-3;

Q is selected from any of CH_3;



and

;

wherein

R^4, R^5 and R^6 is each and independently selected from any of

(i) C_6-C_{10} aryl; or

(ii) heteroaryl having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; and

wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined above;

(iii) a straight or branched C_1-C_6 alkyl or C_2-C_6 alkenyl;

(iv) C_1-C_3 alkoxy;

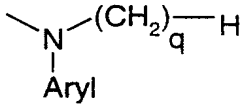
(v) saturated or unsaturated C_3 - C_6 cycloalkyl, optionally and independently substituted by one or more aryl groups or heteroaryl groups having from 5 to 10 atoms with the heteroatom(s) being selected from any of S, N and O and wherein the aryl, heteroaryl and cycloalkyl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined above;

(vi) -[$(CH_2)_q$-aryl] where q is an integer of from 1-3, and the aryl may optionally be substituted by 1 or 2 substituents Y, where each Y is as defined above;

(vii) -[$(CH_2)_r$-heteroaryl] where r is an integer of from 1-3, the heteroaryl having from 5 to 10 atoms with heteroatoms(s) being selected from any of S, N, and O, optionally and independently substituted by 1 or 2 substituents Y as defined above;

(viii) -[CH_2-O-aryl] where the aryl may optionally be substituted by 1 or 2 substituents Y, where each Y is as defined above;

(ix)



where q is an integer of from 1-2, and the aryl is as defined below, optionally substituted by 1 or 2 substituents Y, where each Y is as defined above;

R^1 is selected from anyone of

(i) a straight or branched C_1-C_6 alkyl or C_2-C_6 alkenyl, where each alkyl and alkenyl may optionally be substituted by one or more aromatic or heteroaromatic substituents;

(ii) C_3-C_7 cycloalkyl, optionally comprising one or more unsaturations and optionally substituted by one or more of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, hydroxy; or substituted by one or more aryl(s), or heteroaryl(s) having from 5 to 10 atoms and the heteroatom(s) being selected from any of S, N and O and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined above;

(iii) hydrogen, halogen or C_1-C_6 alkoxy;

(iv) C_6-C_{10} aryl;

(v) heteroaryl having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined above;

(vi) 9,10-dihydro-9,10-ethanoantracenyl;

(vii) -[$(CH_2)_q$-aryl] where q is an integer of from 1-3 and the aryl may optionally be substituted by 1 or 2 substituents Y, where each Y is as defined above;

(viii) -[$(CH_2)_r$-heteroaryl] where r is an integer of from 1-3, the heteroaryl having from 5 to 10 atoms and the heteroatoms(s) being selected from any of S, N, and O, and wherein the heteroatom(s) may optionally and independently be substituted by 1 or 2 substituents Y, where each Y is as defined above;

(ix) -[$(CH_2)_q$-aryl-O-$(CH_2)_r$-aryl] where q and r is each and independently an integer of from 1-3;

(x) -$(CH_2)_q$-[C_3-C_6 cycloalkyl] where q is from 1-2, optionally substituted by 1 or 2 substituents Y and wherein Y is as defined above;

R^2 is selected from any of

(i) hydrogen;

(ii) a straight or branched C_1-C_6 alkyl or C_2-C_6 alkenyl, where each alkyl and alkenyl may optionally be substituted by one or more aromatic or heteroaromatic substituents;

(iii) C_6 - C_{10} arylalkyl, wherein the aryl may optionally be substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined above;

(iv) heteoaryl-(C_5 - C_{10} alkyl), where the heteroaryl has from 5 to 10 atoms and the heteroatom being selected from any of S, N and O, and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined above;

(v) C_3-C_{10} cycloalkyl, optionally comprising one or more unsaturations and optionally susbtituted by one or more heteroaryl(s) where the heteroaryl has from 5 to 10 atoms and the heteroatom being selected from any of S, N and O;
and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined above;

(vi) C_6-C_{10} aryl, optionally and independently substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom(s) being selected from any of S, N and O and wherein the heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined above;

(vii) heteroaryl having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined above;

R^3 is selected from anyone of

(i) hydrogen;

(ii) a straight or branched C_1-C_6 alkyl or C_2-C_6 alkenyl, where each alkyl and alkenyl may optionally be substituted by one or more aromatic or heteroaromatic substituents;

(iii) C_6 - C_{10} arylalkyl, wherein the aryl may optionally be substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined above;

(iv) heteoaryl-(C_5 - C_{10} alkyl), where the heteroaryl has from 5 to 10 atoms and the heteroatom being selected from any of S, N and O, and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined above;

(v) C_3-C_6 cycloalkyl, optionally comprising one or more unsaturations and optionally substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O, and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined above;

(vi)

;

wherein

R^7, R^8, R^9, R^{10} and R^{11} is each and independently selected from

(a) hydrogen;

(b) a straight or branched C_1-C_6 alkyl or C_2-C_6 alkenyl, where each alkyl and alkenyl may optionally be substituted by one or more aromatic or heteroaromatic substituents;

(c) C_6 - C_{10} arylalkyl, wherein the aryl may optionally be substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined above;

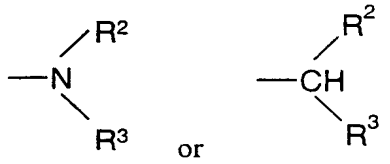
(d) heteoaryl-(C_5 - C_{10} alkyl), where the heteroaryl has from 5 to 10 atoms and the heteroatom being selected from any of S, N and O, and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined above;

(e) C_3-C_{10} cycloalkyl, optionally comprising one or more unsaturations and optionally susbtituted by one or more heteroaryl(s) where the heteroaryl has from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined above;

(f) C_6-C_{10} aryl, optionally and independently substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom(s) being selected from any of S, N and O and wherein the heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined above.

Particularly preferred compounds according to the invention are compounds of the formula (I) wherein

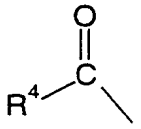
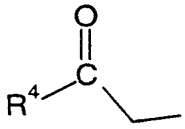
A is



wherein R^2 and R^3 are as defined below;

Z is $(CH_2)_m$ or a carbonyl group;

m and n are each and independently 1 or 2;

Q is  or 

wherein

R^4 is selected from

(i) phenyl;

(ii) heteroaryl having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; wherein the phenyl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined above;

(iii) cyclohexyl;

(iv) C_1-C_6 alkyl;

(v) C_1-C_3 alkoxy;

R^1 is

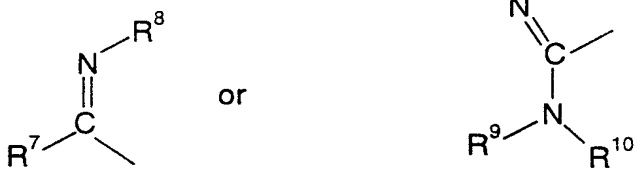
(i) -[$(CH_2)_q$-aryl] where q is an integer of from 1-3 and the aryl may optionally be substituted by 1 or 2 substituents Y, where each Y is as defined above; or

(ii) C_3-C_7 cycloalkyl, optionally comprising one or more unsaturations and optionally substituted by one or more of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, hydroxy; or substituted by one or more aryl(s), or heteroaryl(s) having from 5 to 10 atoms and the heteroatom(s) being selected from any of S, N and O and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined above;

(iii) -(CH_2)-cyclohexyl;

R^2 is hydrogen;

R^3 is



wherein R^7, R^8, R^9, R^{10} and R^{11} are as defined above.

Examples of heterocyclic ring systems which may be formed by R^2 and R^3 together include but are not limited to azeridine, pyrrolidine, piperidine, azepine, azocine, their hydrogenated or dehydrogenated derivatives, their aminoderivatives and other aza-heterocycle moieties and their derivatives, such as dihydroimidazoles, di-, tetra- and hexahydropyrimidines and the like.

By "halogen" we mean chloro, fluoro, bromo and iodo.

By "aryl" we mean an aromatic ring having 6 or 10 carbon atoms, such as phenyl and naphthyl.

By "heteroaryl" we mean an aromatic ring in which one or more of the from 5-10 atoms in the ring are elements other than carbon, such as N, S and O.

By "isomers" we mean compounds of the formula (I), which differ by the position of their functional group and/or orientation. By "orientation" we mean stereoisomers, diastereoisomers, regioisomers and enantiomers.

By "isoforms" we mean compounds of the formula I which differ in the relative physical arrangement of molecules by crystal lattice, such that isoforms refer to various crystalline compounds and amorphous compounds.

By "prodrug" we mean pharmacologically acceptable derivatives, e.g. esters and amides, such that the resulting biotransformation product of the derivative is an active form of the drug. The reference by Goodman and Gilmans, The Pharmacological basis of Therapeutics, 8th ed., McGraw-Hill, Int. Ed. 1992, "Biotransformation of Drugs, p. 13-15, describing prodrugs generally, is hereby incorporated by reference.

The novel compounds of the present invention are useful in therapy, especially for the treatment of various pain conditions such as chronic pain, acute pain, cancer pain, pain caused by rheumatoid arthritis, migraine, visceral pain etc. This list should however not be interpreted as exhaustive.

Compounds of the invention are useful as immunomodulators, especially for autoimmune diseases, such as arthritis, for skin grafts, organ transplants and similar surgical needs, for collagen diseases, various allergies, for use as anti-tumour agents and anti viral agents.

Compounds of the invention are useful in disease states where degeneration or dysfunction of opioid receptors is present or implicated in that paradigm. This may involve the use of isotopically labelled versions of the compounds of the invention in diagnostic techniques and imaging applications such as positron emission tomography (PET).

Compounds of the invention are useful for the treatment of diarrhoea, depression, urinary incontinence, various mental illnesses, cough, lung oedema, various gastro-intestinal disorders, spinal injury and drug addiction, including the treatment of alcohol, nicotine, opioid and other drug abuse and for disorders of the sympathetic nervous system for example hypertension.

Compounds of the invention are useful as an analgesic agent for use during general anaesthesia and monitored anaesthesia care. Combinations of agents with different properties are often used to achieve a balance of effects needed to maintain the anaesthetic state (eg. Amnesia, analgesia, muscle relaxation and sedation). Included in this combination are inhaled anaesthetics, hypnotica, anxiolytics, neuromuscular blockers and opioids.

The compounds of the present invention in isotopically labelled form are useful as a diagnostic agent.

Also within the scope of the invention is the use of any of the compounds according to the formula (I) above, for the manufacture of a medicament for the treatment of any of the conditions discussed above.

A further aspect of the invention is a method for the treatment of a subject suffering from any of the conditions discussed above, whereby an effective amount of a compound according to the formula (I) above, is administered to a patient in need of such treatment.

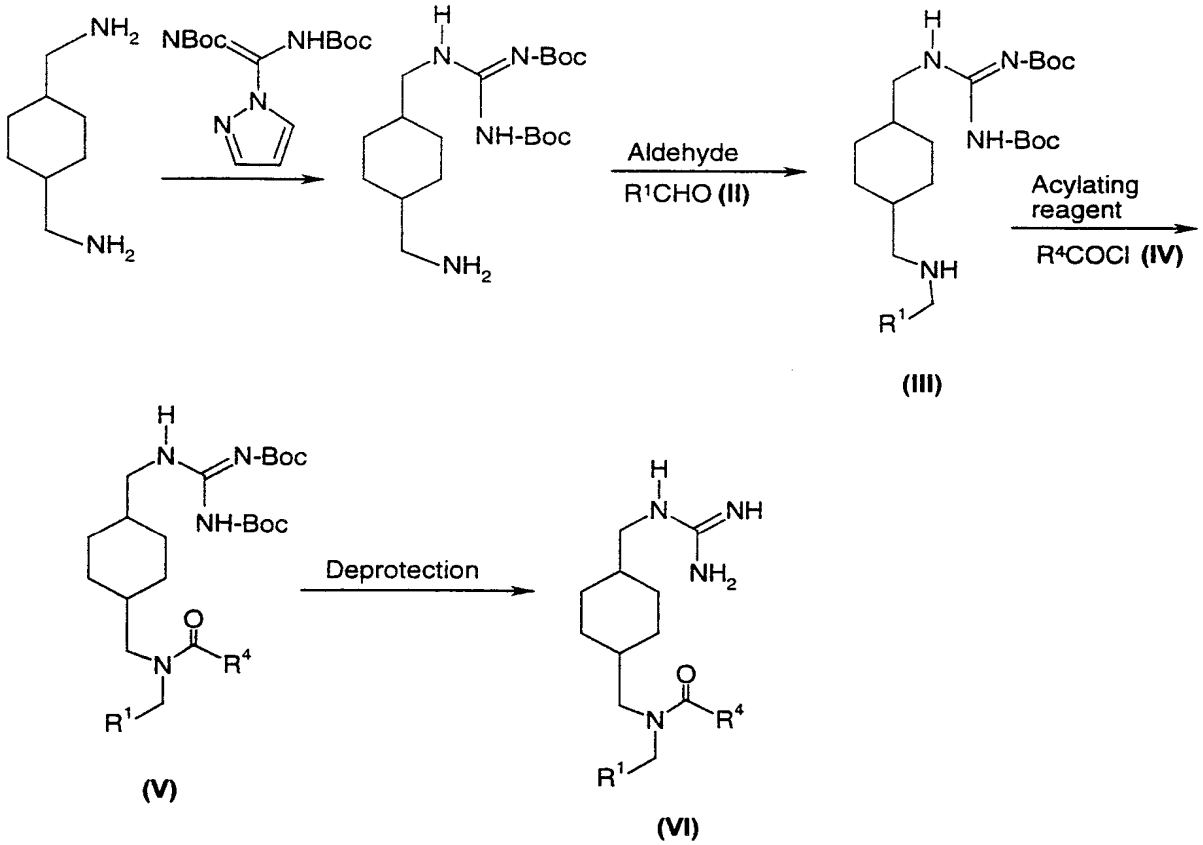
The best mode of performing the invention known at present, is to use the compounds according to Example 9 (compound 14), Example 14 (compound 30) and Example 53 (compound 120). The numbering of the compounds is in accordance with the numbering in the Schemes presented in the following.

Methods of preparation

Compounds of the formula I, as described above, may be obtained by following the procedures described below.

Preparation of 1,4-cis,trans-cyclohexane derived compounds

SCHEME I



The compounds of general formula **(VI)** may be prepared by following the procedure described in Scheme I above.

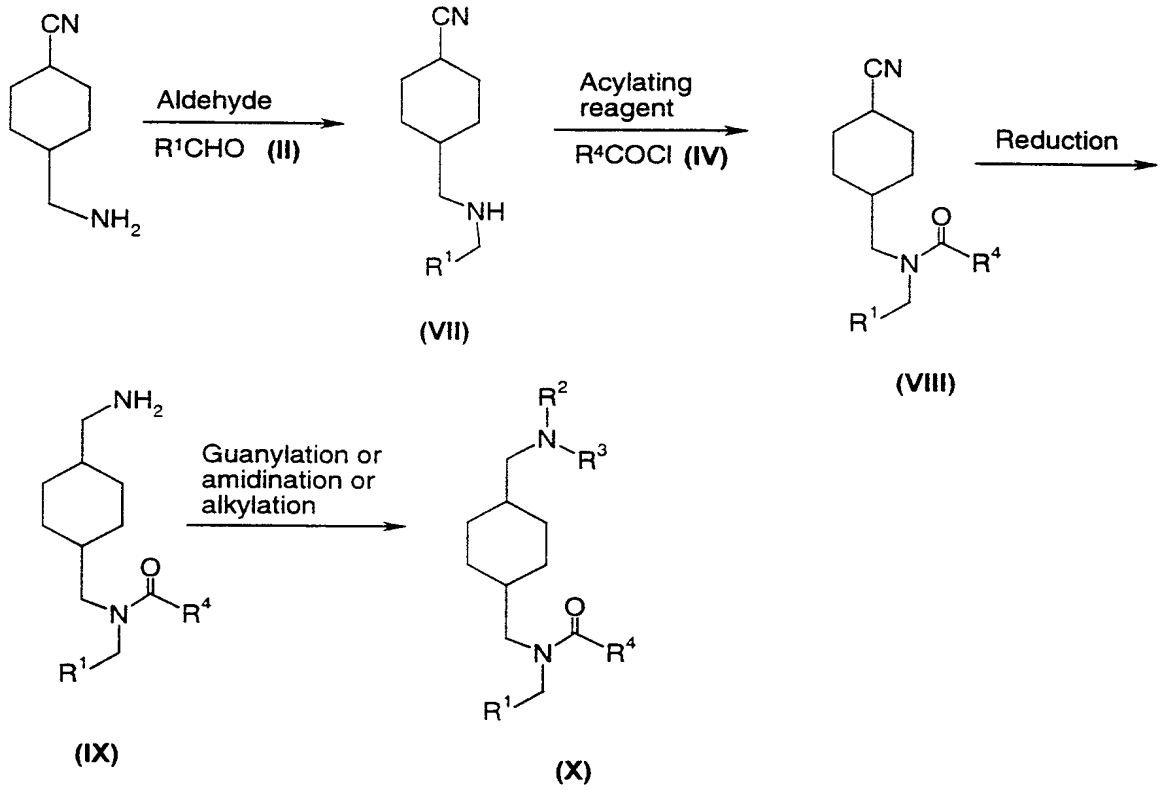
Commercially available cis/trans-mixtures of 1,4-bis-aminomethyl cyclohexane is converted to mono-(diBoc)guanidinomethyl derivative, using a protected guanylating reagent such as 1-H-pyrazole-1-(N,N-bis(tert-butoxycarbonyl)carboxamidine in an organic solvent such as THF. The secondary amine **(compound III)** can be generated using a reductive amination step where **compound III** is reacted with an aldehyde **(compound II)** such as C_1-C_6 alkylaldehyde or phenylaldehyde in the presence of an acid such as acetic acid or $ZnCl_2$ in a protic solvent such as methanol or ethanol in the presence of a reducing agent such as sodiumcyanoborohydride.

Compounds of the general **formula (V)** may be obtained by performing an acylating reaction where **compound III** is mixed with an acid chloride **(compound IV)** or other appropriate acylating agent such as acid anhydride in a solvent such as methylene chloride and in the presence of a tertiary amine as base, such as triethylamine.

Finally, compounds of the general **formula (VI)** may be obtained by cleavage of the Boc protecting groups with an acid such as aqueous hydrochloric acid, or by using organic acid such as trifluoroacetic acid in a solvent such as methylene chloride.

In the formulas **(III), (IV), (V)** and **(VI)** in Scheme I above, R^1 and R^4 are as defined in formula I of claim 1.

SCHEME II



Alternatively, compounds of the general **formula (X)** may be obtained as described in Scheme II above.

Cis,trans-4-(aminomethyl)-cyclohexane carbonitrile is reacted with an aldehyde in the presence of a reducing agent such as sodium cyanoborohydride in a protic solvent such as methanol, and in the presence of an acid such as acetic acid or alternatively a Lewis acid such as zinc chloride.

Compounds of the general **formula (VIII)** may be prepared by acylating the remaining secondary amines of **compound (VII)** using an acylating reagent such as benzoyl chloride in an organic solvent such as methylene chloride in the presence of a base such as triethylamine.

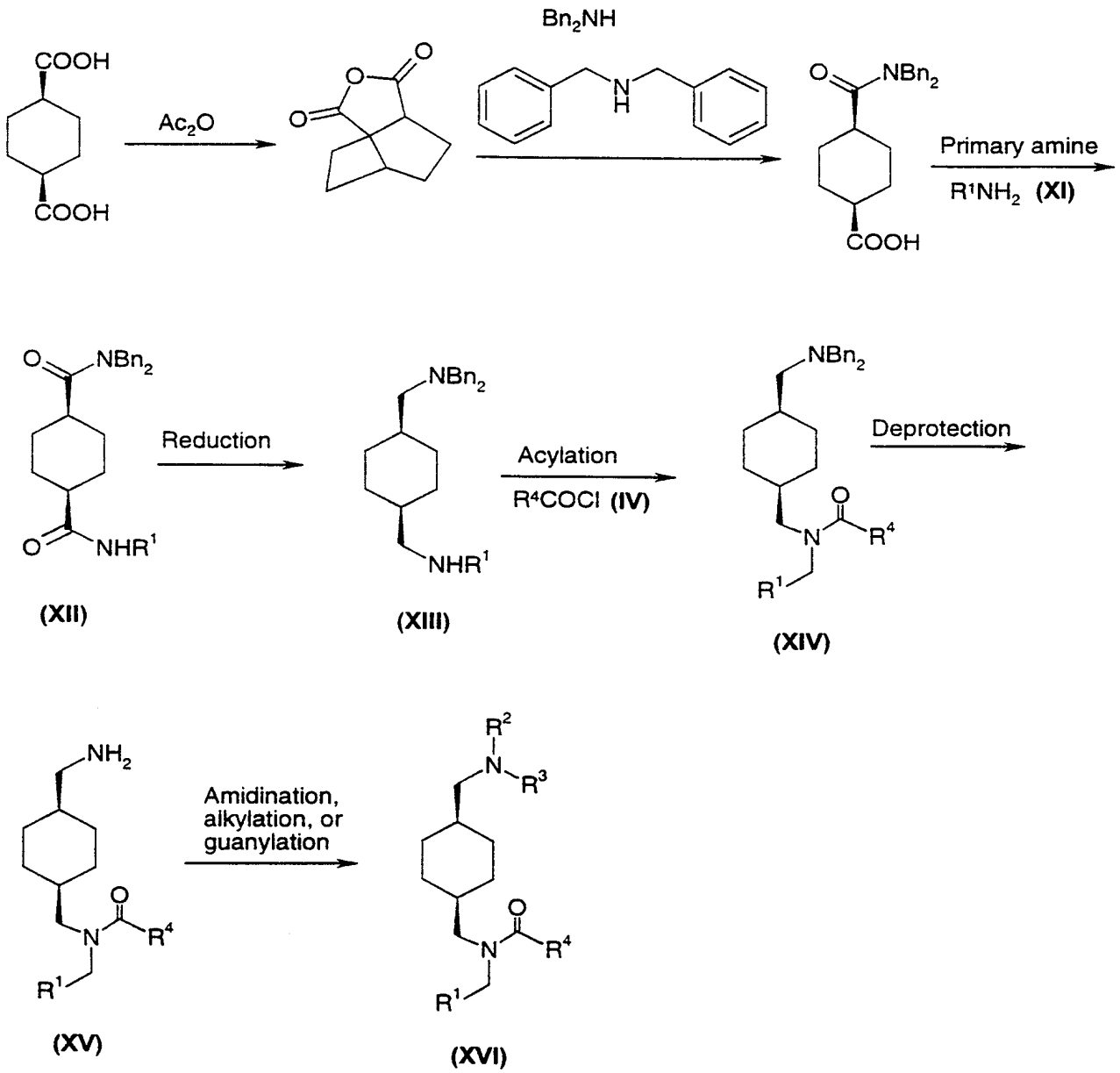
The primary amine of the general **formula (IX)** may be obtained by reducing the nitrile group in **compound (VIII)** using hydrogen in the presence of a catalyst such as 10 % Pd on carbon in an organic solvent such as ethanol.

Compounds of the general **formula (X)** may be prepared by guanylation, amidination or alkylation in an organic solvent such as methanol and DMF in the presence of an organic base such as triethylamine.

In the formulas **(VII), (VIII), (IX)** and **(X)** in Scheme II above, R^1 and R^4 are as defined in formula I above.

Preparation of 1,4-cis-cyclohexane derived compounds

SCHEME III



5

The 1,4-cis-cyclohexane derived compounds of the general **formula (XVI)** may be obtained by following the reaction sequence in **Scheme III** above.

The cis-1,4-cyclohexane dicarboxylic acid anhydride is prepared according to H.K. Halt (J. Org. Chem. 2027, 1963). The anhydride is then reacted with dibenzylamine to generate the corresponding cis-acid amide.

Compounds of the general **formula XII** may be obtained by reacting the acid functionality with a primary amine of **formula XI** in the presence of a tertiary amine base such as di-isopropylethylamine in an organic solvent such as DMF. Both carbonyl groups are then reduced to generate compounds of the general **formula (XIII).** The use of a reducing reagent such as BH_3-THF in an organic solvent such as THF effectively reduces both amides.

Compounds of the general **formula (XIV)** may be obtained by using an acylating reagent such as benzoyl chloride in an organic solvent such as methylene chloride in the presence of a base such as triethylamine.

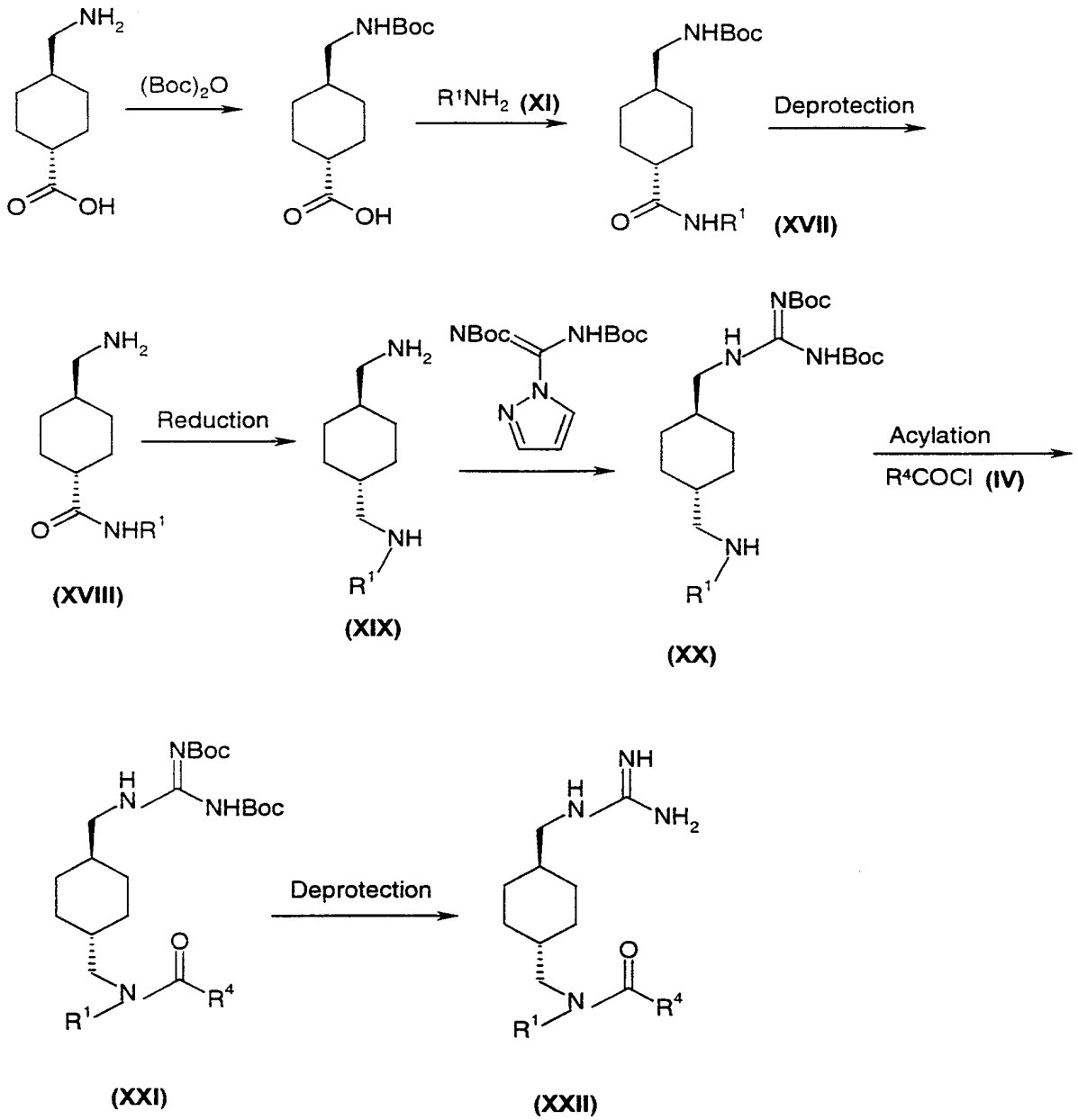
Compounds of the general **formula (XV)** may be obtained by cleavage of the benzyl groups using a reduction reaction such as hydrogenation. The hydrogenation is performed in the presence of a catalyst such as 10 % Pd on carbon in a solvent such as acetic acid and using a pressure of 50 psi.

Compounds of the general **formula (XVI)** may be obtained by reacting the primary amine of the **formula (XV)** with a guanylating reagent such as 1-H-pyrazole-1-(N,N-bis(tert-butoxycarbonyl))carboxamidine, or with an amidinating reagent or by alkylation, in a solvent such as THF or DMF.

In the formulas **(IV), (XI), (XII), (XIII), (XIV), (XV), and (XVI),** in Scheme III above, R^1, R^2, R^3 and R^4 are as defined in formula I above.

Preparation of trans-guanidinomethyl cyclohexane derived compounds

SCHEME IV



The trans-guanidinomethyl cyclohexane derived compounds of the general **formula (XXII)** may be obtained as shown in **Scheme IV** above.

Commercially available trans-4-aminomethyl cyclohexane carboxylic acid is protected using either di-tert-butyl dicarbonate or benzoyl chloride, followed by amidation using a primary amine of the **formula (XI)** in an organic solvent such as methylene chloride in the presence of a coupling reagent such as BOPCl and a tertiary amine base such as triethylamine, providing compounds of the general **formula (XVII)**. Cleavage of the Boc-protecting groups may be effected using an organic acid such as trifluoroacetic acid in an organic solvent such as methylene chloride, providing compounds of the **formula (XVIII).**

Compounds of the **formula (XIX)** may be obtained by using a reduction procedure consisting of using a hydride source such as a Borane complex in an organic solvent such as THF. Compounds of the **formula (XX)** may be obtained by reacting the primary amine in **(XIX)** with a guanylating reagent such as 1-H-pyrazole-1-(N,N-bis(tert-butoxycarbonyl)carboxamidine in an organic solvent such as THF. Acylation of the remaining secondary amine in **XX** with an acylating reagent **IV** such as benzoyl chloride in an organic solvent such as dioxane or methylene chloride in the presence of a base such as triethylamine, providing compounds of the general **formula (XXI).**

A deprotection step of **(XXI)** with an acid such as trifluoroacetic acid or an aqueous solution of hydrochloric acid, provides compounds of the general **formula (XXII).**

In Scheme IV above, R^1 and R^4 are as defined in formula I above.

EXAMPLES

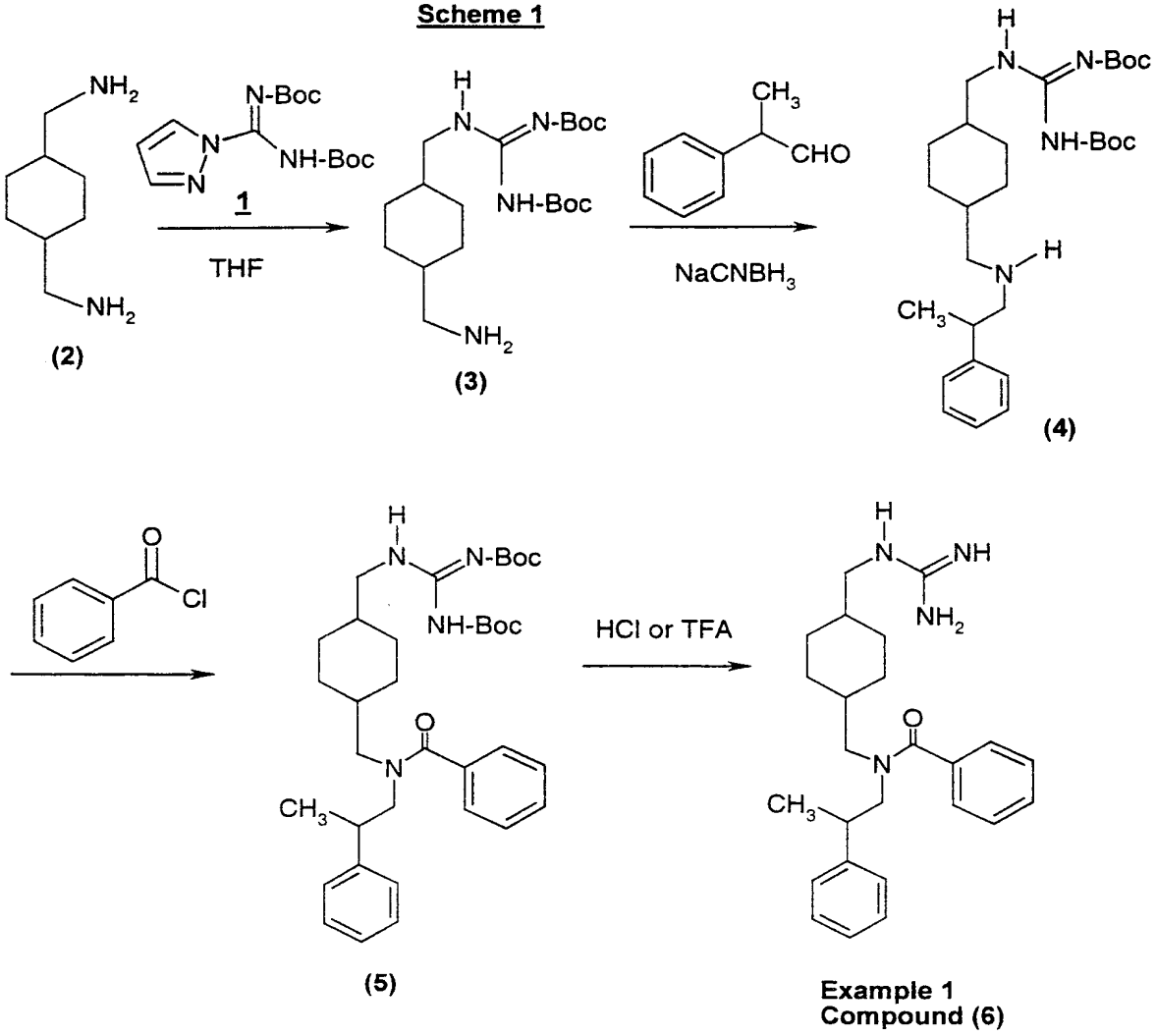
The invention will now be described in more detail by way of the following general procedures and specific examples, which should not in any way be regarded as limiting the invention.

EXAMPLE 1

Preparation of 1-[(N-benzoyl)-N-(1-methyl-1-phenyl-ethyl)]-aminomethyl-4-guanidinomethylcyclohexane hydrochloride (compound 6)

Compound 6 of Example 1 was prepared by following the synthetic route described in **Scheme 1** below.

Scheme 1



Example 1
Compound (6)

Preparation of 1-(diBoc)-guanidinomethyl-4-aminomethyl cyclohexane

Part A

1-H-pyrazole-1-carboxamidine was prepared according to *Bernatowicz et.al., J. Org. Chem. 1992, 57, pp.2497-2502*, and protected with di-tert-butyl dicarbonate to give 1-H-pyrazole-1-(N,N-*bis*(tert-butoxycarbonyl)carboxamidine (**compound 1**) according to *Drake et.al, Synth. 1994. pp.579-582.*

Part B

Step 1

Preparation of 1-(diBoc)-guanidinomethyl-4-aminomethyl cyclohexane (compound 3)

To a solution of 1,4-*bis*-aminomethyl-cyclohexane (**compound 2**) (20 g, 0.14 mol) in THF (200 mL) was added a solution of 1-H-Pyrazole-1-(N,N-*bis*(tert-butoxycarbonyl)carboxamidine (**compound 1**) (22.0 g, 0.07 mol) in THF (100 mL). The solution was stirred at room temperature for 3 hrs. The solvent was removed under reduced pressure to give a syrupy residue which was taken up in ethyl acetate and washed with water until neutral pH. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The product (**compound 3**) was purified by column chromatography on silica gel using a mixture of methylene chloride:methanol as the eluent to afford 11.6 g (43 % yield) of **1-(diBoc)-guanidinomethyl-4-aminomethyl cyclohexane**, i.e. **compound 3.**

^1H NMR ($CDCl_3$) δ 3.26 (d of t, 2H), 2.52 (d of d, 2H), 1.82-0.97 (m, 28H, with singlet at 1.5).

Step 2

Preparation of 4-N-(diBoc)guanidinomethyl-1-N-(1-methyl-1-phenylethyl)-aminomethylcyclohexane (compound 4)

To a solution of **1-(diBoc)-guanidinomethyl-4-aminomethyl cyclohexane (compound 3)** (1 eq) in methanol containing 1% (v/v) of glacial acetic acid (alternatively, $ZnCl_2$ can be

used) was added 2-methyl-phenylacetaldehyde (1 eq), followed by $NaBH_3CN$ (3-4 eq). The reaction mixture was stirred at room temperature overnight. The reaction was quenched with water, basified with aqueous $NaHCO_3$ solution and extracted with methylene chloride. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The product (**compound 4**) was chromatographed on silica gel using a mixture of hexane:ethyl acetate as the eluent.

Step 3

Preparation of 4-N-(diBoc)-guanidinomethyl-1-(N-benzoyl)-N-(1-methyl-1-phenylethyl)-aminomethylcyclohexane (compound 5)

To a solution of **compound 4** prepared in step 2 (1 eq) in dioxane or methylene chloride, was added triethylamine (1.5-2.0 eq), followed by benzoyl chloride (1 eq). The reaction mixture was stirred at room temperature for 3 h, then basified with 1N K_2CO_3 solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, concentrated and chromatographed on silica gel or purified by preparative TLC using a mixture of hexane-ethyl acetate as the eluent.

Step 4

Preparation of 1-(N-benzoyl)-N-(1-methyl-1-phenylethyl)-aminomethyl-4-guanidinomethyl cyclohexane (compound 6)

The diBoc-guanidino compound (**compound 5**) was dissolved in 4N HCl in dioxane or 50% trifluoroacetic acid in methylene chloride and stirred at room temperature for 2 h. The solvent was removed under reduced pressure. The residue was dissolved in water and lyophylized. The product (**compound 6**) can also (when appropriate) be purified by reversed-phase HPLC using acetonitrile-water as the eluent.

Step 5

Preparation of 1-(N-benzoyl)-N-(1-methyl-1-phenylethyl)-aminomethyl-4-guanidinomethyl cyclohexane hydrochloride (compound 6 x HCl)

To a mixture of the base compound 6 prepared in Step 4 (2 mmol) in methylene chloride (10 ml) and methanol (10 ml) was added a solution of HCl (1 M) in ether (8ml, 8 mmol). The reaction mixture was allowed to stir at room temperature for 2 h. The volatile was removed under vacuum and the resulting solid dried under vacuum to give the corresponding hydrochloride salt.

MS(APCI): 407.06 (M + H)

Examples 2-11

Examples 2 to 11 (compounds 7 to 16) were prepared as described for compound 6 of Example 1, using the reagents in the respective Examples as described in Table 1 below.

Table 1

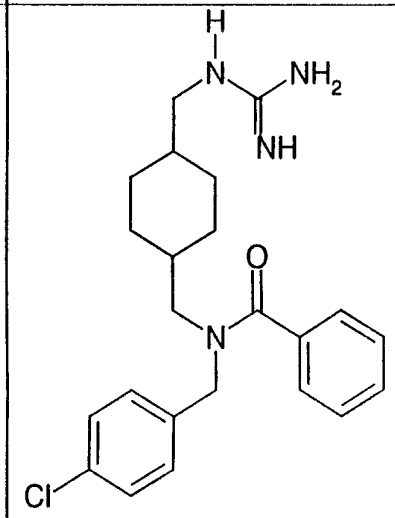
Ex	Structure	Chemical name	(i) Aldehyde (ii) Acid chloride	Physical Characterization
2	 **Compound 7**	1-[N-Benzoyl-N-(p-chlorobenzyl)]-aminomethyl-4-guanidinomethylcyclohexane x HCl	(i) 4-chlorobenzaldehyde (ii) Benzoyl chloride	**MS(APCI):** 413.01 (M+H).

Table 1 (contd.)

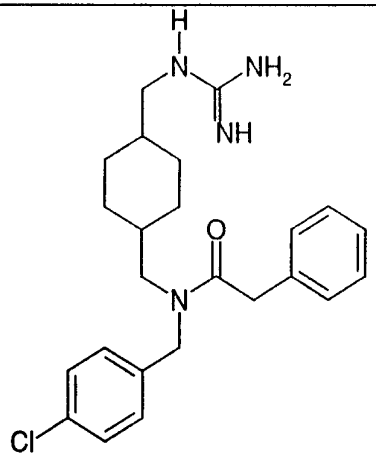
Ex	Structure	Chemical name	(i) Aldehyde (ii) Acid chloride	Physical Characterization
3	 **Compound 8**	1-[N-(p-chlorobenzyl)-N-(phenylacetyl)]-aminomethyl-4-guanidinomethyl cyclohexane x HCl	(i) 4-chlorobenzaldehyde (ii) Phenyl acetylchloride	**MS(APCI):** 427.02 (M+H)

Table 1 (Contd.)

Ex	Structure	Chemical name	(i) Aldehyde (ii) Acid chloride	Physical Characterization
4	 **Compound 9**	1-[N-(p-Chlorobenzyl)-N-(2,2-diphenylethyl)]-aminomethyl-4-guanidinomethyl-cyclohexane x HCl	(i) Diphenylacetaldehyde (ii) 4-chlorobenzoyl chloride	**MS(APCI):** 503.08 (M+H).

Table 1 (Contd.)

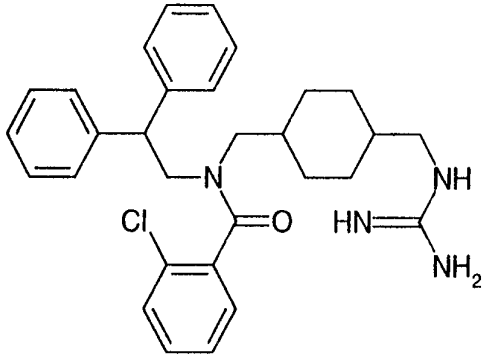
Ex	Structure	Chemical name	(i) Aldehyde (ii) Acid chloride	Physical Characterization
5	 **Compound 10**	1-[N-(o-chlorobenzoyl)-N-(2,2-diphenylethyl)]-aminomethyl-4-guanidinomethyl cyclohexane x HCl	(i) Diphenylacetaldehyde (ii) 2-chlorobenzoyl chloride	**^{1}H NMR (pyridine)** δ 7.10-7.50 (m, 14H), 5.05 (m, 1H), 4.55 (b, 2H), 4.1 (t, 1H), 3.95 (t,1H,) 3.75 (m, 2H), 3.3 (t, 1H), 3.15 (m, 2H), 0.8-1.8 (m, 10 H). **MS(APCI):** 503.08 (M+H).

Table 1 (Contd.)

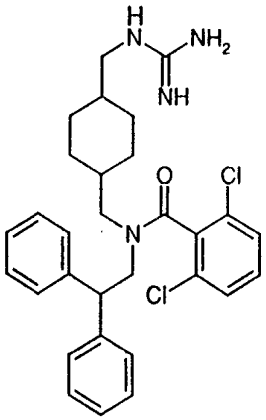
Ex	Structure	Chemical name	(i) Aldehyde (ii) Acid chloride	Physical Characterization
6	 **Compound 11**	1-[N-(2,2-diphenylethyl)-N-(2,6-dichlorobenzoyl)]-aminomethyl-4-guanidinomethyl cyclohexane x HCl	(i) Diphenylacetaldehyde (ii) 2,6-dichlorobenzoyl chloride	**^{1}H NMR (pyridine)** δ 7.10-7.50 (m, 13H), 4.9 (m, 1H), 4.55 (m, 2H), 4.1 (t, 1H), 3.75 (m, 2H), 3.05-3.3 (m, 3H), 0.8-1.95 (m, 10 H). **MS(APCI):** 536.95 M+H).

Table 1 (Contd.)

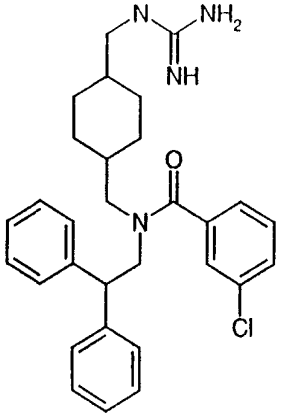
Ex	Structure	Chemical name	(i) Aldehyde (ii) Acid chloride	Physical Characterization
7	 **Compound 12**	1-[N-(2,2-Diphenylethyl)-N-(m-chlorobenzoyl)]-aminomethyl-4-guanidino-methylcyclohexane	(i) Diphenylacetaldehyde (ii) 3-chlorobenzoyl-chloride	**MS(APCI):** 503.05 (M+H).

Table 1 (Contd.)

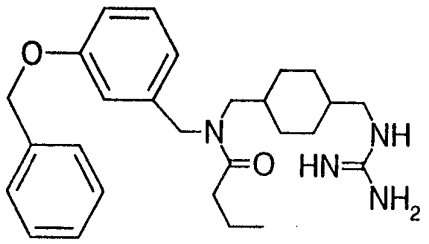
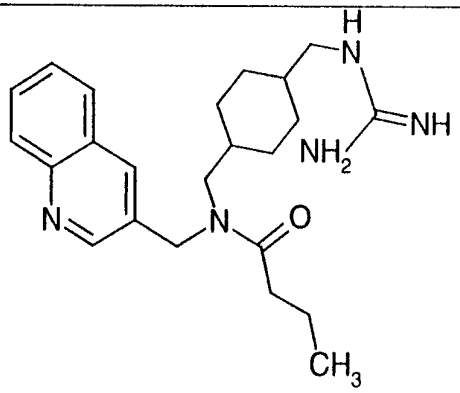
Ex	Structure	Chemical name	(i) Aldehyde (ii) Acid chloride	Physical Characterization
8	 **Compound 13**	1-[(N-butyroyl)-N-(3'-benzyloxy)-benzyl]-aminomethyl-4-guanidinomethylcyclohexane	(i) 3-benzyloxy benzaldehyde (ii) n-butanoyl chloride	**^{1}H NMR ($CDCl_3$)** δ 7.80 (b, 1H), 7.37 (m, 5H), 6.72 (m, 4H), 5.06 (s, 2H), 4.49 (s, 2H), 3.34 (d, 2H), 3.08 (t, 3H), 2.28 (t, 3H), 1.43 (m, 12H), 1.17 (t, 3H). **MS (APCI):** 451 (M+H). HRMS calcd for $C_{27}H_{38}N_4O_2$ 451.3013, observed 451.3053.

Table 1 (Contd.)

Ex	Structure	Chemical name	(i) Aldehyde (ii) Acid chloride	Physical Characterization
9	 **Compound 14** *cis/trans mixture*	1-[N-(3-Quinolinemethyl)-N-(butyroyl)]-aminomethyl-4-guanidinomethyl cyclohexane	(i) 3-quinaldehyde (ii) n-butanoyl chloride	**^{1}H NMR (DMSO-d_6)** δ 9.1(d,1H), 8.85 (d, 1H), 8.55 (s, 1H), 8.25 (m, 2H), 8.0 (m, 1H), 7.80 (m, 2H), 4.75 (d, 2H), 3.35 (d, 2H), 3.25 (d, 1H), 3.18 (d, 2H), 2.3 (m, 2H), 1.9 - 0.75 (m, 10H), 0.85 (m, 3H). **MS(ES):** 396 (M+H).

Tabl1 1 (Contd.)

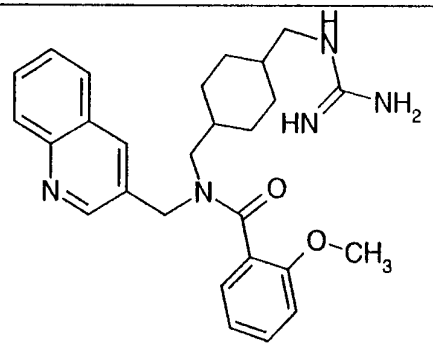
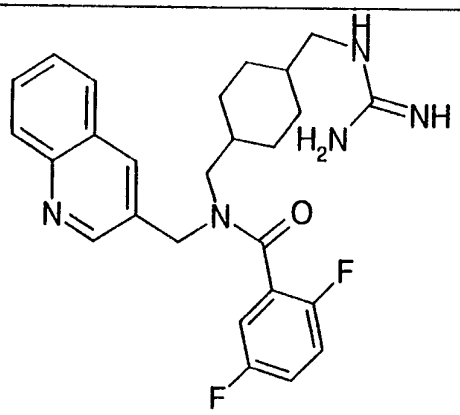
Ex	Structure and Chemical name	Chemical name	(i) Aldehyde (ii) Acid chloride	Physical Characterization
10	 **Compound 15** *cis/trans mixture*	1-[N-(3-Quinolinemethyl)-N-(2-methoxybenzoyl)]-aminomethyl-4-guanidinomethyl-cyclohexane	(i) 3-quinaldehyde (ii) 2-methoxybenzoyl chloride	**^{1}H NMR (DMSO-d_6)** δ 9.25 (s, 1H), 9.0 (d, 1H), 8.35 (t, 1H,) 8.25 (t, 1H), 8.0 (m, 3H), 7.5-6.9 (m, 8H), 4.75 (d, 2H), 3.9 (s, 1.5H), 3.7 (s, 1.5H), 3.2 (d, 1H), 3.1 (d, 1H), 3.0-2.8 (m, 2H), 1.9 - 0.75 (m, 10H). **MS(ES):** 460 (M+H).

Table 1 (Contd.)

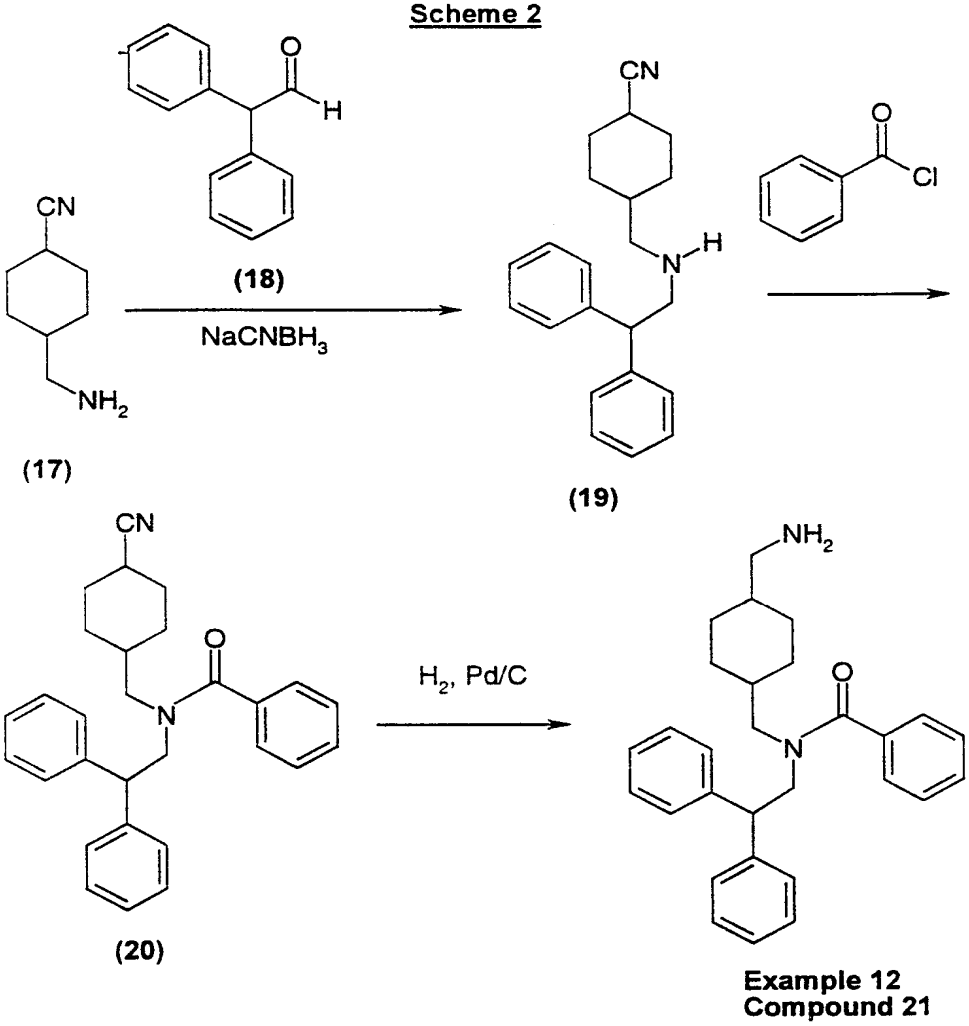
Ex	Structure and Chemical name	Chemical name	(i) Aldehyde (ii) Acid chloride	Physical Characterization
11	 **Compound 16** *cis/trans mixture*	1-[N-(3-Quinolinemethyl)-N-(2,5-difluorobenzoyl)]-aminomethyl-4-guanidinomethyl-cyclohexane	(i) 3-quinaldehyde (ii) 2,5-difluorobenzoyl chloride	**^{1}H NMR (DMSO-d_6)** δ 9.5 (s, 1H), 9.2 (d, 1H), 9.0 (s, 1H), 8.5 (m, 2H), 8.15 (dd, 1H), 8.0 (m, 2H), 7.5-6.9 (m, 8H), 5.1 (s, 1H), 4.8 (s, 1H), 3.7 (s, 1.5H), 3.45-2.95 (m, 4H), 1.9 - 0.75 (m, 10H). **MS(ES):** 466 (M+H).

Example 12

Preparation of cis/trans-1-Aminomethyl-4-[N-2,2-diphenylmethyl)-N-benzoyl]aminomethyl-cyclohexane (compound 21)

The title **compound 21** was prepared by following the synthetic route described in **Scheme 2** below.

Scheme 2



Example 12
Compound 21

Step 1

Preparation of *cis,trans*-4-N-(2,2-diphenylethyl)aminomethyl-cyclohexane carbonitrile (compound 19)

To a methanolic solution (20 mL) of *cis,trans*-4-(aminomethyl)-cyclohexane carbonitrile (**compound 17**) (0.69 g, 5 mmol) and diphenylacetaldehyde (**compound 18**) (0.981, 5 mmol) was added zinc chloride (0.681 g, 5 mmol), and solid sodium cyanoborohydride (0.32 g, 5 mmol). The mixture was stirred overnight under nitrogen. It was diluted with aqueous sodium bicarbonate and extracted with methylene chloride. The organic extracts were washed with brine, dried over $MgSO_4$ and concentrated. The product (**compound 19**) was purified by silica gel chromatography:

Yield: 1.24 g.
MS: 319.03(M+H).

Step 2

Preparation of *cis,trans*-4-[N-(2,2-diphenylethyl)-N-benzoyl]aminomethyl-cyclohexane carbonitrile (compound 20)

To a solution of *cis,trans*-4-N-(2,2-diphenylethyl)aminomethyl-cyclohexane carbonitrile (**compound 19**) prepared in step 1 (0.60 g, 1.89 mmol) in methylene chloride was added triethylamine (0.35 mL) and benzoyl chloride (0.241 mL, 2.07 mmol). The mixture was stirred at r.t. for 3 h., and washed with 5% aq. HCl, saturated sodium bicarbonate, dried over magnesium sulfate and concentrated. The product (**compound 20**) was purified by silica gel chromatography, giving 0.65 g.

Step 3

Preparation of *cis,trans*-1-Aminomethyl-4-[N-(2,2-diphenylethyl)-N-benzoyl]aminomethyl-cyclohexane (compound 21)

A solution of *cis.trans*-4-[N-(2,2-diphenylethyl)-N-benzoyl]aminomethyl-cyclohexane carbonitrile (**compound 20**) prepared in the previous step 2 (0.483 g, 1.14 mmol), was dissolved in a mixture of ethanol (25 mL) and $CHCl_3$ (0.6 mL) and hydrogenated overnight at 50 psi in the presence of 10% Pd/C catalyst (0.10 g). The mixture was filtered through Celite. The filtrate was concentrated and the product (**compound 21**) was purified by silica gel chromatography, using a mixture of methanol/methylene chloride/ammonium hydroxide as the eluent.

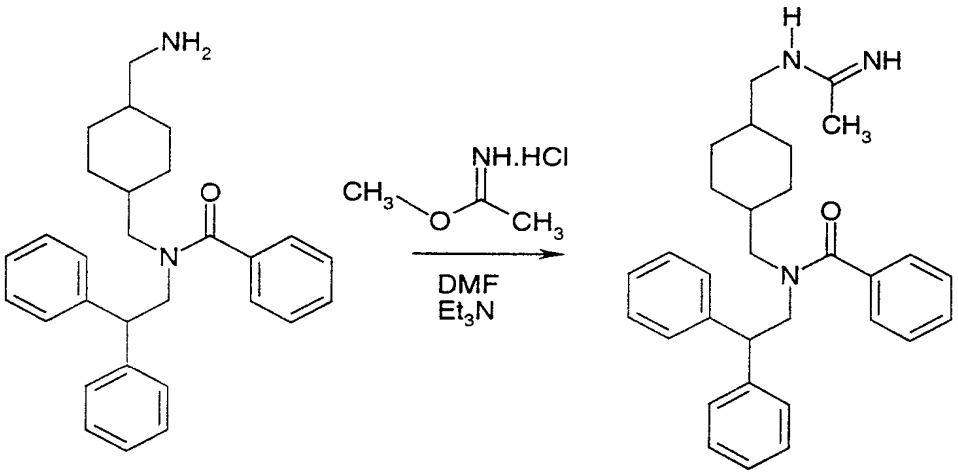
^{1}H NMR ($CDCl_3$) δ 7.65-6.90 (m, 15H), 4.60 (t, 1H), 4.15 (d, 2H), 3.98 (broad s, 1H), 3.37 (broad s, 1H), 2.95- 0.45 (m, 14H). MS(APCI): 427.06 (M+H).

Example 13

Preparation of *cis,trans*-1-Aminomethyl-4-[N-(2,2-diphenylethyl-N-benzoyl]acetamidinomethyl cyclohexane (compound 22)

The title **compound 22** was prepared by following the synthetic routes described in **Scheme 3** below.

Scheme 3



(21)

Example 13
Compound 22

To a solution of **compound 21** (450 mg, 1.05 mmol) in DMF (10 ml) at room temperature was successively added triethylamine (735 µl, 5.28 mmol) and methylacetimidate x HCl (580 mg, 5.28 mmol). The solution was stirred at the same temperature over night, thereafter the solvent was reduced under reduced pressure. The residue was dissolved in dichloromethane, washed with a saturated aqueous sodium chloride solution and extracted several times with dichloromethane. Removal of the solvent from dried organic layers ($MgSO_4$) afforded an oil which was further purified by MPLC with reverse phase silica gel using a solvent gradient (20 - 45 % CH_3CN/H_2O) to give a white crystalline product. The

pure compound was washed with an aqueous sodium hydroxide solution (1 M) and extracted several times with dischloromethane. The combined layers were dried over MgSO4, filtered and concentrated to give the methyl amidine (**compound 22**) (421 mg, 86 %) as a white powder.

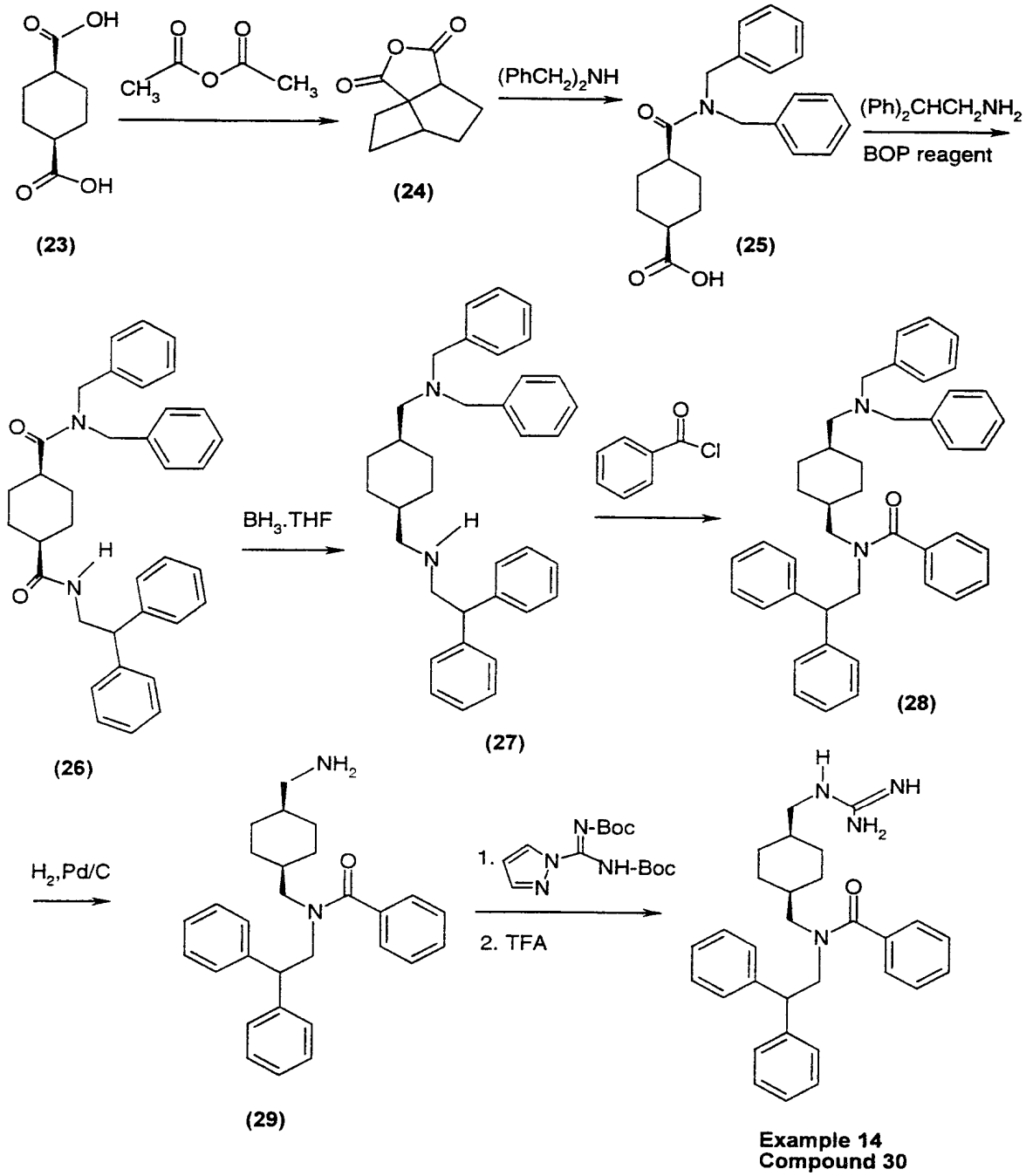
^{1}H NMR (MeOD-d4) δ 7.50-6.90 (m, 15H), 4.60 (broad t, 1H), 4.25-3.95 (m, 3H), 3.47(broad s, 1H), 3.30- 2.72 (m, 6H), 2.18 (s, 3H), 1.98-0.45 (m, H). MS(APCI): 468.10 (M+H).

EXAMPLE 14

Preparation of *cis*-[1-N-(diphenylethyl)-N-benzoyl]aminomethyl-4-N-guanidinomethyl cyclohexane (compound 30)

The title **compound 30** was prepared by following the synthetic routes described in **Scheme 4** below.

Scheme 4



Example 14
Compound 30

Step 1

Preparation of *cis*-4-(N,N-dibenzyl)carboxamido) cyclohexane carboxylic acid (compound 25)

The anhydride was prepared according to literature procedure *[H.K. Hall, J. Org. Chem., 2027 (1963)]*. A mixture of *cis*-1,4-cyclohexane dicarboxylic acid (**compound 23**) (7.0 g, 40.65 mmol) and acetic anhydride (23 g) was heated at reflux for 5 h. Excess acetic anhydride and other volatiles were removed in vacuo under reduced pressure to give an oily residue as **compound 24**.

To this crude anhydride (**compound 24**) was added neat dibenzylamine (8.68 g, 44 mmol) slowly. A viscous solution formed which was diluted with methylene chloride and the solution was stirred overnight. The mixture was then washed with 10% HCl solution, water, brine and then dried over magnesium sulfate. After concentration, the product (**compound 25**) was purified by silica gel column chromatrography, using a mixture of methanol/methylene chloride as the eluent.

MS (APCI): 350.28(M-H).

Step 2

Preparation of *cis*-1-N-(diphenylethyl)-4-(N,N-dibenzyl) cyclohexane dicarboxamide (compound 26)

To an ice-cooled DMF solution (15 mL) of *cis*-4-(N,N-dibenzyl)carboxamido) cyclohexane carboxylic acid (**compound 25**) prepared in the previous step 1 (1.76 g, 5 mmol), was added 2,2-diphenylethylamine (1.03 g, 5 mmol), diisopropylethylamine (2.2 mL, 12.5 mmol), and BOP reagent (2.2 g, 5 mmol). The reaction mixture was stirred overnight. It was diluted with ethyl acetate, and washed with 10% HCl, aqueous sodium bicarbonate solution, brine, dried over magnesium sulfate and concentrated. The product (**compound 26**) was purified by silica gel chromatography, using a mixture of methanol/methylene chloride as the eluent. Yield: 1.30 g.

MS(APCI): 531.26 (M+H).

Step 3

Preparation of *cis*-[1-N-(diphenylethyl)-4-(N,N-dibenzyl)]-bis-aminomethyl cyclohexane (compound 27)

A mixture of *cis*-1-N-(diphenylethyl)-4-(N,N-dibenzyl) cyclohexane dicarboxamide (**compound 26**) prepared in the previous step 2 (1.2 g, 2.26 mmol), and a 1M borane.THF complex (14 mL) was heated at reflux overnight. After cooling to r.t., a 3.3M solution of HCl in methanol (3.6 mL) was added to the reaction mixture and heated at reflux for 2 h. The mixture was then concentrated, diluted with ethyl acetate and washed with aqueous sodium bicarbonate, brine, dried over magnesium sulfate and concentrated to give 1.08 g of product (**compound 27**).

MS(APCI): 503.31 (M+H).

Step 4

Preparation of *cis* -[1-N-(diphenylethyl)-N-benzoyl]-4-(N,N-dibenzyl)]-bis-aminomethyl cyclohexane (compound 28)

A methylene chloride solution of *cis*-[1-N-(diphenylethyl)-4-(N,N-dibenzyl)]-*bis*-aminomethyl cyclohexane (**compound 27**) prepared in the previous step 3 (0.82 g, 1.63 mmol), was acylated with benzoyl chloride (0.21 mL, 1.79 mmol) in the presence of triethylamine (0.454 mL, 3.26 mmol). After 4 h. at r.t., the mixture was washed with sodium bicarbonate solution, brine, dried over magnesium sulfate and concentrated. The product (**compound 28**) was purified by silica gel chromatography, using a mixture of ethyl acetate/hexane as the eluent. Yield: 0.609 g.

MS(APCI): 607.36 (M+H).

Step 5

Preparation of *cis*-[1-N-(diphenylethyl)-N-benzoyl]-4-*bis*-aminomethyl cyclohexane (compound 29)

A solution of *cis*-[1-N-(diphenylethyl)-N-benzoyl]-4-(N,N-dibenzyl)]-*bis*-aminomethyl cyclohexane (**compound 28**) prepared in the previous step 4 (0.77 g, mmol), in glacial acetic acid (25 mL) was hydrogenated at 55 psi in the presence of 10% Pd/C catalyst (0.9 g) for 3 days. The mixture was filtered. The filtrate was concentrated and the product (**compound 29**) was purified by silica gel chromatography.

MS(APCI): 427.24 (M+H).

Step 6

Preparation of *cis*-[1-N-(diphenylethyl)-N-benzoyl]aminomethyl-4-N-guanidinomethyl cyclohexane (compound 30)

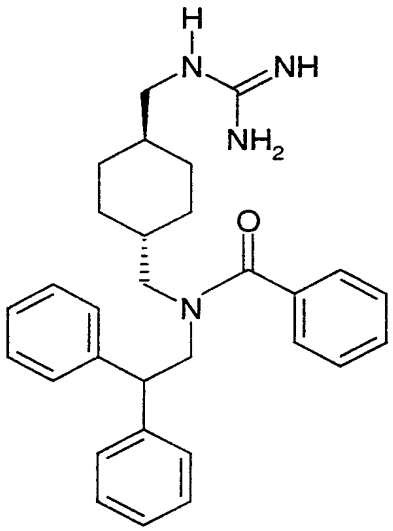
The above product diamine (0.154 g, 0.36 mmol) was dissolved in THF and 1-H-pyrazole-1-(N,N-*bis*(tert-butoxycarbonyl)carboxamidine (0.13 g) was added. The mixture was stirred at r.t. for 2-3 h and then concentrated. The product was purified by silica gel chromatography using ethyl acetate/hexane as the eluent.

cis-[1-N-(diphenylethyl)-N-benzoyl]aminomethyl-4-N-(diBoc)guanidinomethyl-cyclohexane (0.16 g, mmol) was mixed with 50% TFA/CH_2Cl_2 and stirred at r.t. for 2.5 h. The mixture was concentrated. The residue was dissolved in water and lyophilized to give a powder.

MS (APCI): 469.24 (M+H).

EXAMPLE 15

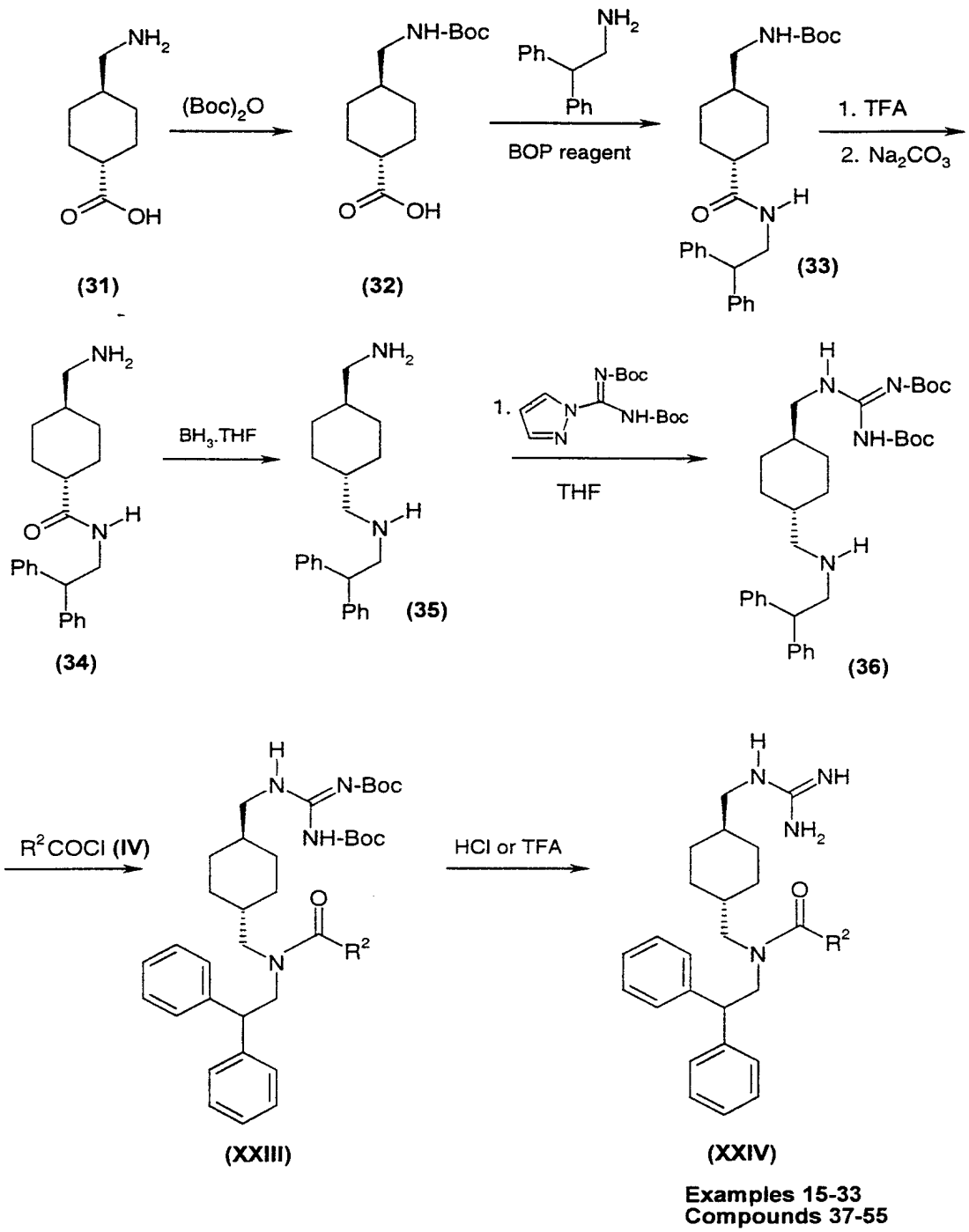
Preparation of *trans*-1-[N-benzoyl-N-(2,2-diphenylethyl)aminomethyl-4-guanidinomethyl cyclohexane] (compound 37)



Compound 37

The title **compound 37** was prepared by following the synthetic routes described in **Scheme 5** below.

Scheme 5



Examples 15-33
Compounds 37-55

Step 1

Preparation of *trans*-4-N-(Boc)aminomethyl cyclohexane carboxylic acid (compound 32)

To an aqueous solution (500 mL) of sodium hydroxide (68 g, 1.7 mol) cooled in an ice bath was added *trans*-4-aminomethyl cyclohexane carboxylic acid (**compound 31**) (150 g, 0.95 mol).

The solution was diluted to 1 liter with acetonitrile. Di-*tert*-butyl dicarbonate (229 g, 1.2 eq) was added portionwise and the mixture was stirred overnight. The acetonitrile was removed by rotary evaporation and the remaining aqueous mixture was extracted with ethyl acetate. The aqueous layer was acidified to pH 3 with $NaHSO_4$, then was extracted with ethyl acetate. The pooled organic extracts were dried over $MgSO_4$ and concentrated to give 224. g of product (**compound 32**) (0.87 mol, 91%).

Step 2

Preparation of *trans*-4-aminomethyl cyclohexane-1-(N-2,2-diphenylethyl) carboxamide (compound 33)

trans-4-N-(Boc)aminomethyl cyclohexane carboxylic acid (**compound 32**) (37 g, .147 mol) was dissolved in methylene chloride (250 mL) and treated with 2,2-diphenylethylamine (29 g, 0.147 mol), benzotriazol-1-yloxy-*tris*(dimethylamino)phosphonium hexafluorophosphate (BOP reagent) (65.1 g, .147 mol), then basified with triethylamine (37.2.g, 0.367 mol, 2.5 eq). After stirring overnight the reaction mixture was washed with water, 10% Na_2CO_3, and 10% $NaHSO_4$, dried over $MgSO_4$ and concentrated to give 76 g of product (**compound 33**).

The product (**compound 33**) was dissolved in methylene chloride (200 mL) and treated with trifluoroacetic acid (200 mL). After stirring for 30 minutes, solvent and excess reagent were removed by rotary evaporation. Water (400 mL) was added and the mixture extracted with ethyl acetate. The aqueous layer was then treated with base to pH 12 and chilled. The precipitated free amine product (**compound 34**) was collected by filtration and dried: 36.2 g (0.108 mol).

MS (APCI): 354 (M+H)

Step 3

Preparation of *trans*-4-aminomethyl-1-N-(2,2-diphenylethyl)aminomethyl cyclohexane (compound 35)

A mixture of the carboxamide (**compound 34**) (15. g, 44.6 mmol) and 1 M solution of borane.THF complex (180 mL) was refluxed overnight. After cooling a solution of HCl in methanol (180 mmol) was added, and the mixture was heated at reflux for 2 h. Excess reagent and solvent were removed under reduced pressure. The residue was dissolved in CH_2Cl_2 and washed with 1 N NH_4OH, brine, dried over $MgSO_4$ and concentrated to give 11.1 g of product (**compound 35**).

Step 4

Preparation of *trans*-4-N-(diBoc)guanidinomethyl-1-[N-(2,2-diphenylethyl)aminomethyl cyclohexane (compound 36)

A mixture of the diamine (**compound 35**) (10. g, 31 mmol) and 1-H-Pyrazole-1-(N,N-*bis*(tert-butoxycarbonyl)carboxamidine (9.6 g, 31 mmol) in THF (100 mL) was stirred at r.t. for 3-5 h. The reaction mixture was concentrated and the product was purified by silica gel chromatography to afford 15 g. of product (**compound 36**).

^{1}H NMR ($CDCl_3$) δ 8.18 (broad s, 1H), 7.44 (s, 1H), 7.43-7.03 (m, 10H), 4.04 (t, 1H), 3.09 (m, 4H), 2.31 (d, 2H), 1.62-1.49 (m, 6H), 1.34 (s, 18 H), 0.77-0.71 (m, 4H).

MS (APCI): 565.36 (M + H), 465.31, 365.20.

Step 5

Preparation of *trans*-4-N-(diBoc)guanidinomethyl-1-N-[N-benzoyl-N-2,2-diphenylethyl)aminomethyl cyclohexane (compound XXIII where R^2= phenyl)

To a solution of secondary amine (compound 36) (1 eq) in dioxane or methylene chloride, was added triethylamine (1.5-2.0 eq), followed by benzoyl chloride (1 eq). The reaction mixture was stirred at room temperature for 3 h, then basified with 1 N K_2CO_3 solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, concentrated and chromatographed on silica gel or purified by preparative TLC using a mixture of hexane-ethyl acetate as the eluent.

Step 6

Preparation of *trans*-1-[N-benzoyl-N-(2,2-diphenylethyl)aminomethyl]-4-guanidinomethyl cyclohexane (compound XXIV where R^2= phenyl)

The diBoc-guanidino compound (**compound XXIII**) was dissolved in 4 N HCl in dioxane or 50 % trifluoroacetic acid in methylene chloride, and stirred at room temperature for 2 h. The solvent was removed under reduced presure. The residue was dissolved in water and lyophilized. The product (**compound XXIV where R^2=phenyl**) may also be purified by reversed-phase HPLC using acetonitrile-water as the eluent.

Examples 16-33

The compounds of Examples 16-23 (**compounds 38-55**) were prepared as described for compound 37 of Example 15, using the reagents in the respective Examples as described in Table 2 below.

Table 2

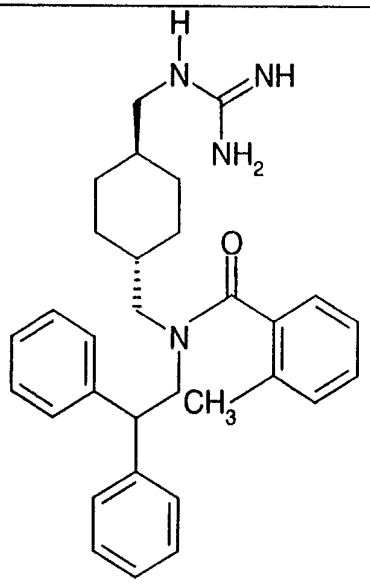
Ex	Structure	Chemical name	Acid chloride	Physical Characterization
16	 **Compound 38**	Trans-1-[N-(2,2-diphenylethyl)-N-(2-methylbenzoyl)]-aminomethyl-4-guanidinomethyl cyclohexane hydrochloride	2-methylbenzoyl chloride	**^{1}H NMR (DMSO-d_6)** δ 0.35-1.50 (m, 10H), 1.70 (s, 3H), 2.45-2.70 (m, 3H), 3.90 (m, 2H), 4.35 (t, 1H), 6.50 (d, 1H), 6.75 (d, 1H), 6.90-7.42 (m, 14H), 7.70 (bs, 1H), 8.50 (bs, 1H). **MS (APCI):** 483 (M+H)

Table 2 (Contd.)

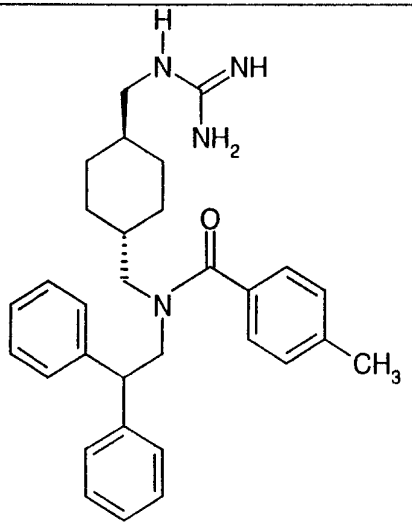
Ex	Structure	Chemical name	Acid Chloride	Physical Characterization
17	 **Compound 39**	Trans-1-[N-(2,2-diphenylethyl)-N-(4-methylbenzoyl)]-aminomethyl-4-guanidinomethyl cyclohexane hydrochloride	4-methylbenzoyl chloride	**^{1}H NMR (DMSO-d_6)** δ 0.50-1.72 (m, 10H), 2.30 (s, 3H), 2.70-2.95 (m, 4H), 4.15 (m, 2H), 4.40 (m, 1H), 6.80-7.45 (m, 16H), 7.75 (s, 1H), 8.60 (bs, 1H). **MS (APCI): 483 (M+H)**

Table 2 (Contd.)

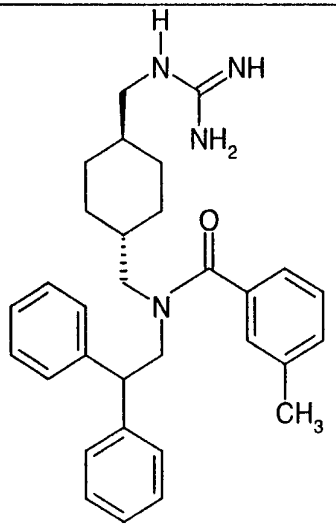
Ex	Structure	Chemical name	Acid Chloride	Physical Characterization
18	 **Compound 40**	Trans-1-[N-(2,2-diphenylethyl)-N-(3-methylbenzoyl)]-aminomethyl-4-guanidinomethyl cyclohexane hydrochloride	3-methylbenzoyl chloride	**^{1}H NMR (DMSO-d_6)** δ 0.50-1.80 (m, 10H), 2.25 (s, 3H), 2.75 (bs, 1H), 3.05 (bs, 2H), 3.25 (m, 1H), 3.90-4.25 (m, 2H), 4.60 (bs, 1H), 6.50-7.40 (m, 16H), 7.85 (bs, 1H), 8.70 (bs, 1H). **MS (APCI):** 483 (M+H).

Table 2 (Contd.)

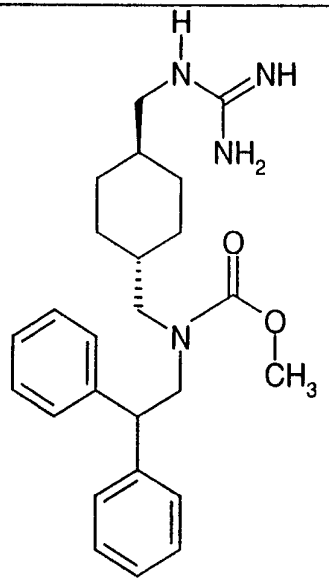
Ex	Structure	Chemical name	Acid Chloride	Physical Characterization
19	 Compound 41	Trans-1-[N-(2,2-diphenylethyl)-N-(methoxyacetyl)]-aminomethyl-4-guanidinomethyl cyclohexane hydrochloride	methoxyacetyl chloride	**^{1}H NMR (DMSO-d_6)** δ 0.92 (m, 4H), 1.40-1.85 (m, 6H), 2.70-3.15 (m, 4H), 3.25 (s, 3H), 3.40 (s, 2H), 4.32-4.50 (m, 1H), 7.15-7.40 (m, 10H). **MS (APCI):** 437 (M+H).

Table 2 (contd.)

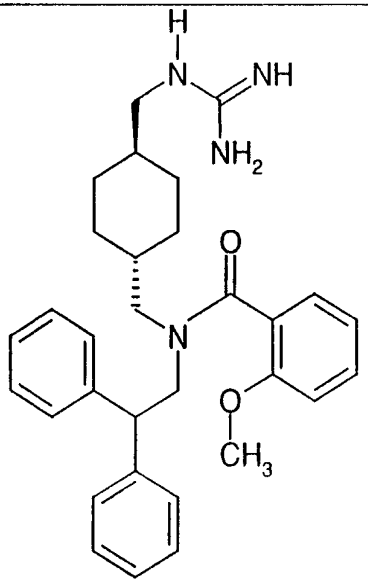
Ex	Structure	Chemical name	Acid Chloride	Physical Characterization
20	 **Compound 42**	Trans-1-[N-(2,2-diphenylethyl)-N-(2-methoxybenzoyl)]-aminomethyl-4-guanidinomethyl cyclohexane hydrochloride	2-methoxy benzoyl chloride	**^{1}H NMR (DMSO-d_6)** δ 0.25 (t, 1H), 0.61 (m, 3H), 1.02 (m, 1H), 1.20 (m, 2H), 1.42-1.63 (m, 3H), 2.50-3.10 (m, 4H), 3.02 (d, 1H), 3.40 (s, 1.5H), 3.65 (s, 1.5H), 3.80-3.90 (m, 2H), 4.35 (t, 1H), 6.60-7.20 (m, 14H), 7.60 (d, 1H), 8.20 (bs, 2H). **MS (APCI):** 499 (M+H)

Table 2 (contd.)

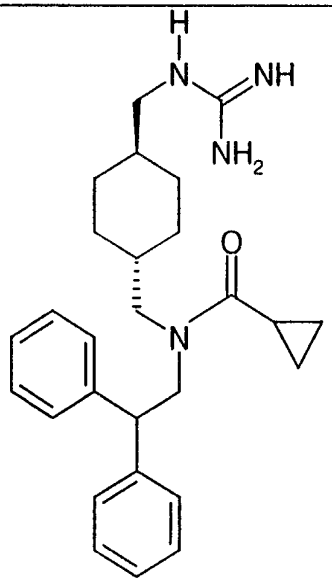
Ex	Structure	Chemical name	Acid Chloride	Physical Characterization
21	 **Compound 43**	Trans-1-[N-(2,2-diphenylethyl)-N-(cyclopropylcarbonyl)]-aminomethyl-4-guanidinomethyl cyclohexane hydrochloride	cyclopropane carbonyl chloride	**^{1}H NMR (DMSO-d_6)** δ 0.30-0.72 (m, 7H), 1.15-1.76 (m, 8H), 2.71 (m, 4H), 3.71 (d, 1H), 3.90 (d, 1H), 4.15 (dd, 1H), 6.90-7.20 (m, 10H), 7.72 (bs, 1H), 9.60 (bs, 1H). **MS (APCI):** 433 (M+H)

Table 2 (Contd.)

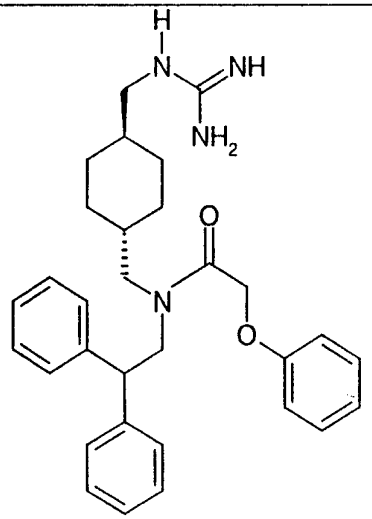
Ex	Structure	Chemical name	Acid Chloride	Physical Characterization
22	 **Compound 44**	Trans-1-[N-(2,2-diphenylethyl)-N-phenoxyacetyl]-aminomethyl-4-guanidinomethyl cyclohexane hydrochloride	phenoxyacetyl chloride	**^{1}H NMR (DMSO-d_6)** δ 0.60 (m, 4H), 1.10--1.25 (m, 2H), 1.51 (m, 4H), 2.60 (d, 1H), 2.75 (d, 2H), 3.02 (d, 1H), 3.80 (t, 2H), 4.22 (s, 2H), 4.45 (s, 1H), 6.30 (d, 1H), 6.55 (d, 1H), 6.72-7.30 (m, 13H), 7.60 (bs, 1H), 9.20 (bs, 1H). **MS (APCI):** 433 (M+H).

Table 2 (contd.)

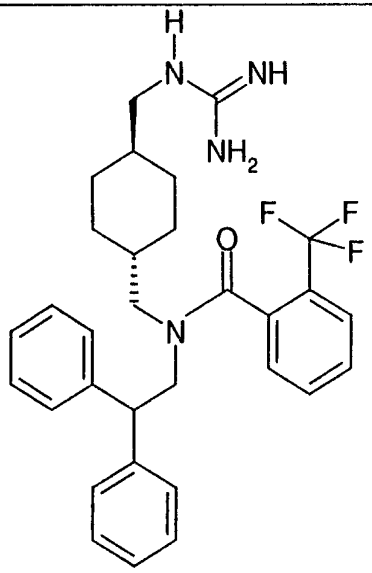
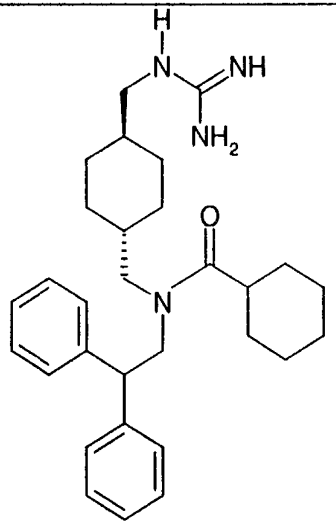
Ex	Structure	Chemical name	Acid Chloride	Physical Characterization
23	 **Compound 45**	Trans-1-[N-(2,2-diphenylethyl)-N-(2-trifluoromethylbenzoyl)-aminomethyl]-4-guanidinomethyl cyclohexane hydrochloride	2-trifluoromethyl benzoyl chloride	**^{1}H NMR (DMSO-d_6)** δ 0.30 (m, 1H), 0.62 (m, 13H), 0.95-1.25 (m, 2H), 1.30-1.62 (m, 4H), 2.30 (d, 1H), 2.72 (m, 3H), 3.20 (dd, 1H), 3.85 (dd, 1H), 4.20 (dd, 1H), 6.20-7.81(m, 15H). **MS (APCI):** 537 (M+H).

Table 2 (Contd.)

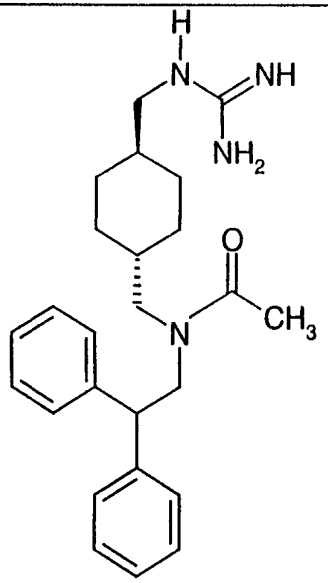
Ex	Structure	Chemical name	Acid Chloride	Physical Characterization
24	 **Compound 46**	Trans-1-[N-(2,2-diphenylethyl)-N-(cyclohexylcarbonyl)]-aminomethyl-4-guanidinomethyl cyclohexane hydrochloride	cyclohexane carbonyl chloride	**^{1}H NMR (DMSO-d_6)** δ 0.50-1.62 (m, 21H), 2.55 (d, 1H), 2.85 (bs, 2H), 2.93 (d, 1H), 3.64(dd, 2H), 4.01 (dd, 1H), 6.81-7.30 (m, 12H), 7.50 (bs, 1H), 8.30 (bs, 1H). **MS (APCI):** 474 (M+H).

Ex	Structure	Chemical name	Acid Chloride	Physical Characterization
25	Compound 47	trans-1-[N-(2,2-diphenylethyl)-N-(butyroyl)]- aminomethyl-4-guanidinomethyl-cyclohexane hydrochloride	n-butanoyl chloride	**MS**: 435.42 (M+H).

Ex	Structure	Chemical name	Acid Chloride	Physical Characterization
26	Compound 48	Trans-1-[N-(2,2-diphenylethyl)-N-(2-furanoyl)]-aminomethyl-4-guanidinomethyl cyclohexane hydrochloride	2-furoyl chloride	MS: 459 (M+H).

Ex	Structure	Chemical name	Acid Chloride	Physical Characterization
27	Compound 49	Trans-1-[N-(2,2-diphenylethyl)-N-(2-thiophenecarbonyl)]-aminomethyl-4-guanidinomethyl-cyclohexane hydrochloride	2-thiophenecarbonyl chloride	**MS:** 475 (M+H).

Table 2 (Contd.)

Ex	Structure	Chemical name	Acid Chloride	Physical Characterization
28	 **Compound 50**	Trans-1-[N-(2,2-diphenylethyl)-N-(acetyl)]aminomethyl-4-guanidinomethyl cyclohexane hydrochloride	acetyl chloride	**^{1}H NMR (DMSO-d_6)** δ 0.60 (m, 5H), 1.12-1.47 (m, 5H), 1.46 (s, 3H), 2.48 (d, 1H), 2.71(m, 3H), 3.68 (t, 2H), 4.03 (t, 1H), 4.14 (t, 1H), 6.54-7.28 (m, 13H), 7.67(d, 1H). **MS (APCI):** 407 (M+H).

Ex	Structure	Chemical name	Acid Chloride	Physical Characterization
29	Compound 51	Trans-1-[(N-2,2-diphenylethyl)-N-(2-chlorobenzoyl)]-aminomethyl-4-guanidinomethyl cyclohexane hydrochloride	2-chlorobenzoyl chloride	**^{1}H NMR (DMSO-d$_6$)** δ 7.52-6.65 (m, 14H), 4.36 (t, 1H), 3.98 (broad t, 2H), 3.70-2.3 (m, 4H), 1.65-0.2 (m, 10H). **MS:** 503.24 (M+H).

Table 2 (Contd.)

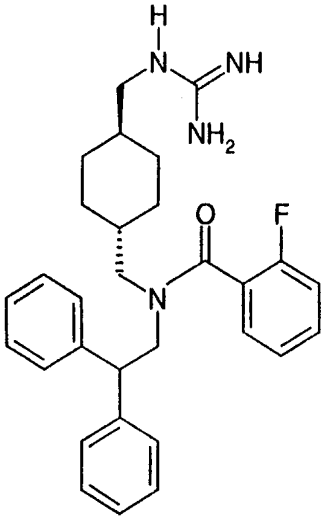
Ex	Structure	Chemical name	Acid Chloride	Physical Characterization
30	 **Compound 52**	Trans-1-[(N-2,2-diphenylethyl)-N-(2-fluorobenzoyl)]-aminomethyl-4-guanidinomethyl cyclohexane hydrochloride	2-fluorobenzoyl chloride	**^{1}H NMR (DMSO-d_6)** δ 7.50-6.60 (m, 14H), 4.30 (t, 1H), 3.85 (broad t, 2H), 3.68 (d or dd, 1H), 2.70 (d of t, 2H), 2.41 (d or dd, 1H), 1.65-0.15 (m, 10H). **MS:** 487.26 (M+H).

Table 2 (Contd.)

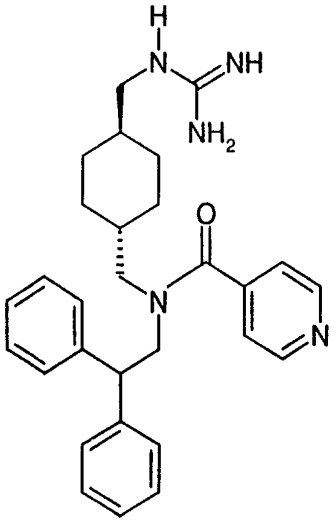
Ex	Structure	Chemical name	Acid Chloride	Physical Characterization
31	 **Compound 53**	Trans-[N-(isonicotinoyl)-N-(2,2-diphenylethyl)]-aminomethyl-4-guanidinomethyl cyclohexane hydrochloride	isonicotinoyl-chloride	**^{1}H NMR (MeOD-d_4)** δ 8.9 (d,1H), 8.75 (d,1H), 7.25-7.60 (m, 10H), 7.1 (d,2H), 4.75 (t, 1H), 4.4 (t, 1H), 4.25 (m, 2H), 4.0 (d, 1H), 3.15 (m, 2H), 2.85 (d, 2H), 0.8-1.95 (b, 10 H). **MS(APCI):** 470.29 (M+H).

Table 2 (Contd.)

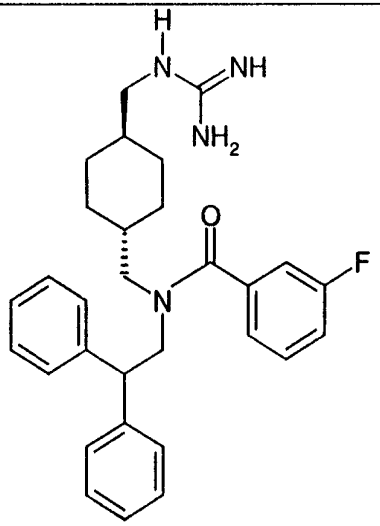
Ex	Structure	Chemical name	Acid Chloride	Physical Characterization
32	 **Compound 54**	Trans-1-[N-(2,2-Diphenylethyl)-N-(3-fluorobenzoyl)]-aminomethyl-4-guanidinomethyl cyclohexane hydrochloride	3-fluorobenzoyl chloride	**MS:** 487.26 (M+H).

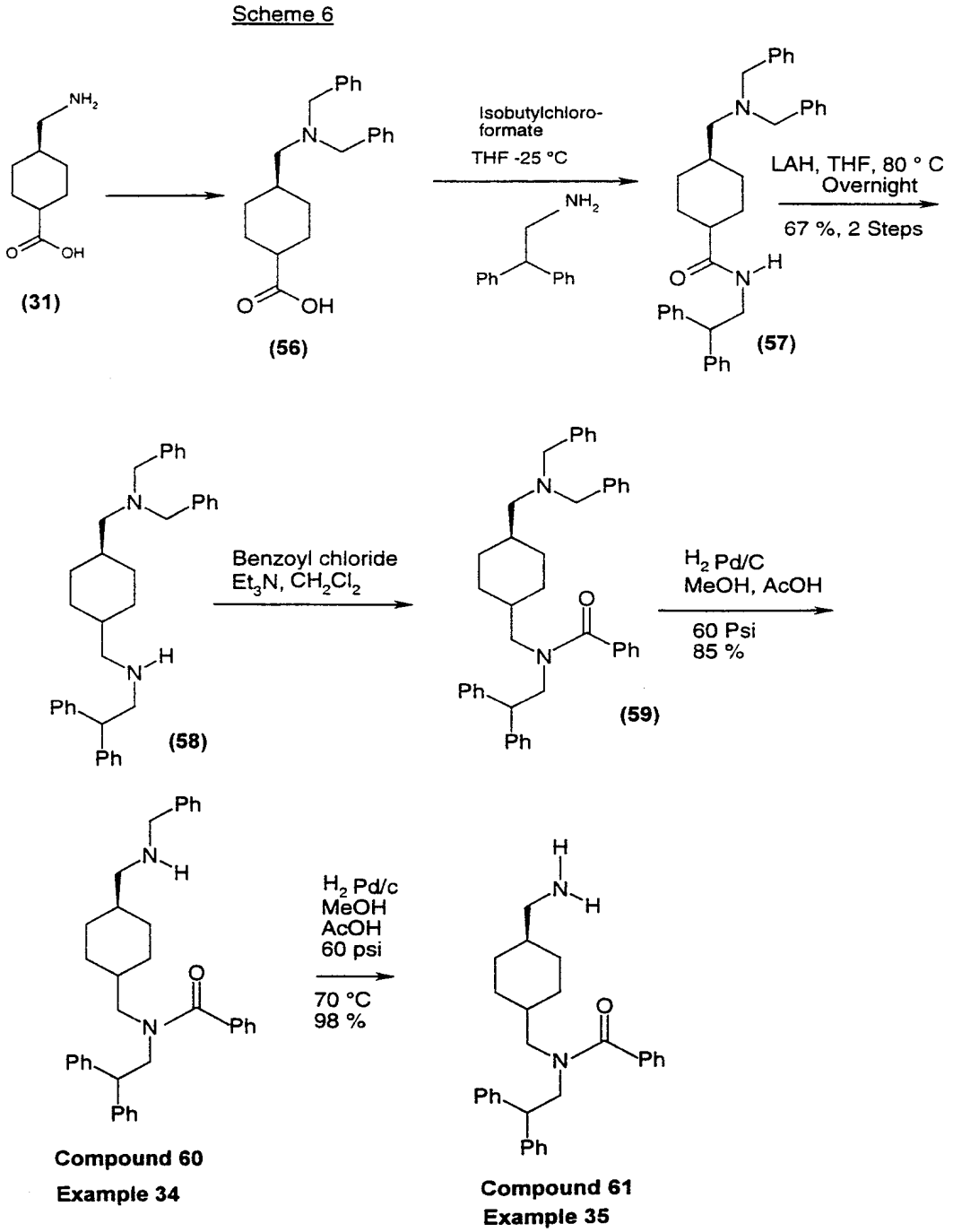
Table 2 (Contd.)

Ex	Structure	Chemical name	Acid Chloride	Physical Characterization
33	Compound 55	Trans-1-[N-(2,2-Diphenylethyl)-N-(4-fluorobenzoyl)]-aminomethyl-4-Guanidinomethyl cyclohexane Hydrochloride	4-fluorobenzoyl chloride	**MS:** 487.26 (M+H).

Examples 34-35

The **compounds 60 and 61** of Examples 34 and 35 were prepared by following the synthetic procedure described in **Scheme 6** below.

Scheme 6



Example 34

Preparation of trans-1-[(N-Benzoyl-N-(2,2-diphenylethyl)]-aminomethyl]-4-(N-benzyl)-aminomethyl cyclohexane (compound 60)

Step 1

Preparation of *trans*-4,N,N-(Dibenzyl)-aminomethyl cyclohexane carboxylic acid (compound 56)

To a suspension of (40.0 g, 254 mmol) of *trans*-4-(Aminomethyl)cyclohexanecarboxylic (**compound 31**) acid, in 1.5 L of methanol was added benzaldehyde (60 ml, 590 mmol) followed by sodium cyanoborohydride (16g, 254 mmol). The pH was then adjusted to approx. 5 with glacial acetic acid. The reaction was allowed to stir for 48 hrs, during which the pH is monitored and adjusted to 5 as needed, after which the reaction volume was then decreased and the pH adjusted to 9 with 1 N NaOH. The reaction was then extracted repeatedly with diethyl ether. The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated. The resulting product solidifies on standing and was recrystallized from methanol giving 32 g of impur product (**compound 56**) which was used without further purification in the next step.

The monobenzyl was isolated as a white solid which formed during the extraction and was collected by filtration. (8.2g)

Monobenzyl ^{1}H NMR: (D_2O) δ (ppm): 7.40-7.20 (5H, m, Ar), 4.06 ($C\underline{H}_2Ar$, 5H, s), 2.75 (2H, d, J=7.2, $NC\underline{H}_2$), 1.95-1.85 (1H, m), 1.75-1.72 (2H, m), 1.64-1.62 (2H, m), 1.56-1.51 (1H, m), 1.22-1.11 (2H, m), 0.91-0.81 (2H, m).

^{13}C NMR: (D_2O, DSS) δ (ppm): 31.43 (CH_2), 31.88 (CH_2), 36.81 (CH), 48.95 (CH), 54.01 (NCH_2), 55.35 (NCH_2), 131.94 (CH), 132.37 (CH), 132.60 (CH), 133.30 (C), 188.43 (C=O).

Step 2

Preparation of *trans*-4-N,N-(Dibenzyl)-aminomethyl cyclohexane-1-(N-2,2-diphenylethyl) carboxamide (57)

To a solution of (**compound 56**) prepared in the previous step 1 (5,3 g, 15,72 mmol), in dry THF (75 ml) at -25 °C, was added triethylamine (2.63 ml, 18.87 mmol) followed by isobutylchloroformate (2.45 ml, 18.87 mmol). The reaction mixture was stirred 30 min at 25 °C. A white pricipitate was formed during the reaction. The 2,2-diphenylethylamine (4.65 g, 23.58 mmol) was added. The reaction mixture was warmed up to r.t., stirred for 3h30 and quenched with saturated aqueous NH_4Cl solution, and extracted with CH_2Cl_2. The organic layer was dried over anhydrous $MgSO_4$ and concentrated to give a crude product (**compound 57**), which was further purified by silica gel column chromatography using CH_2Cl_2 to give a white powder which was used directly to the next step.

^{1}H NMR: ($CDCl_3$, TMS) δ (ppm): 7.47-7.19 (20H, m Ar), 5.30 (1H, m, NH), 4.17-4.14 (1H, m, CH), 3.88-3.80 (2H, m, CH_2N), 3.49 (4H, s, CH_2Ph), 2.16-2.14 (2H, m, CH_2N), 1.91-1.43 (6H, m), 1.33-1.28 (2H, m). 0.69-0.64 (2H, m).

Step 3

Preparation of *trans*-4-N,N-(Dibenzyl)-aminomethyl-1-(N-2,2-diphenylethyl) aminomethyl cyclohexane(compound 58)

To a solution of crude product (**compound 57**) (6.19 g, 11.9 mmol) in dry THF (150 ml) at r.t was added LAH (6.83 g, 180 mmol). The mixture was heated at reflux 80 °C overnight. The mixture was then cooled down at r.t. quenched with MeOH at 0 °C until no hydrogen formation evolved and 1 N HCl was added to dissolve the precipitate formed. The gray mixture was extracted with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to give the crude product which was further purified by MPLC using CH_2Cl_2MeOH (97:3) to provide the titled compound (**compound 58**) (4.15 g, 67%) as a white powder.

^{1}H NMR: ($CDCl_3$, TMS) δ (ppm): 7.35-7.18 (20H, m, Ar), 4.19(1H, t, C<u>H</u>), 3.49 (4H, s, C<u>H</u>$_2$ Ph), 3.19 (2H, d, C<u>H</u>$_2$N), 2.45 (2H, d, C<u>H</u>$_2$N), 2.16 (2H, d, C<u>H</u>$_2$N), 1.87-1.84 (2H, m), 1.65-1.62 (2H, m), 1.52 (2H, m), 1.27 (1H, s, br, N<u>H</u>), 0.90-0.64 (4H, m).

<u>Step 4</u>

<u>Preparation of *trans*-4-N,N-(Dibenzyl)-aminomethyl-1-(N-2,2-diphenylethyl) aminomethyl cyclohexane benzamide (compound 59)</u>

To a solution of (**compound 58**) prepared in the previous step 3 (4.1 g, 8.17 mmol), in dry CH_2Cl_2 at r.t., was added triethylamine (2.27 ml, 16.34 mmol) and benzoyl chloride (1.19 ml, 9.8 mmol). The reaction mixture was stirred 1 h at r.t. then the solvent was removed under reduced pressure. The resulting crude product (**compound 59**) was further purified by silica gel column chromatography using hexane-AcOEt (9:1~1:1) to give (4.14 g, 84 %) of title product as a white powder.

^{1}H NMR: ($CDCl_3$, TMS) δ (ppm): 7.34-7.20 (22H, m, Ar), 7.20-6.98 (3H, m, Ar), 4.59-4.4.55 (1H, m, C<u>H</u>), 4.13-3.94 (2H, m, C<u>H</u>$_2$N), 3.51-3.33 (4H, m, C<u>H</u>$_2$Ph), 2.78-2.76 (2H, m, C<u>H</u>$_2$N), 2.19-2.13 (2H, m, C<u>H</u>$_2$N), 1.92-1.25 (6H, m), 0.90.51 (4H, m).

<u>Step 5</u>

<u>Preparation of *trans*-4-N-(Benzyl)-aminomethyl-1-(N-2,2-diphenylethyl) aminomethyl cyclohexane benzamide (compound 60)</u>

To a solution of (**compound 59**) prepared in the previous step 4 (870mg, 1.44 mmol), in AcOH (10ml) and MeOH (10 ml), was added palladium on activated carbon 10 % (187 mg). The mixture was stirred overnight at r.t. with 60 psi of hydrogen. The mixture was then filtered over celite pad and the solvent was removed under reduced pressure. The resulting mixture was dissolved in CH_2Cl_2 and extracted with saturated aqueous $NaHCO_3$ solution. The organic layer was dried over anhydrous $MgSO_4$ and concentrated to give the crude product (**compound 60**) which was further purified by silica gel chromatography using CH_2Cl_2-MeOH (9:1) to provide the desired product as a clear oil (631 mg, 85 %).

^{1}H NMR: ($CDCl_3$, TMS) δ (ppm): 7.43-7.23 (17H, m, Ar), 6.96-6.94 (3H, m, Ar), 4.60-4.55 (1H, m, C<u>H</u>), 4.20-3.95 (2H, m, C<u>H</u>$_2$N), 3.79 (2H, s, br, C<u>H</u>$_2$Ph), 3.20 (1H, s, br C<u>H</u>$_2$N), 2.85-2.79 (1H, m, C<u>H</u>$_2$N), 2.59-2.53 (2H, m, C<u>H</u>$_2$N), 1.90-1.20 (5H, m),1.30 (1H, s, br), 1.10-0.90 (2H, m), 0.65-0.50 (2H, m).

<u>Example 35</u>

<u>Preparation of *trans*-4-Aminomethyl-1-(N-2,2-diphenylethyl)-aminomethyl cyclohexane benzamide (compound 61)</u>

The **compound 60** (3.2 g, 6.25 mmol) was dissolved in AcOH (20 ml) and MeOH (20 ml) and Palladium on activated carbon (10 %) (546 mg) was added to the solution. The mixture was stirred overnight with 60 psi of hydrogen, then 4h at 70 °C. The mixture was then cooled down and filtered over celite pad and the solvent removed under reduced pressure. The crude product was dissolved in CH_2Cl_2 and the organic phase washed with saturated aqueous $NaHCO_3$ solution. The organic layer was dried over anhydrous MgSO4 and concentrated to give the pure desired product (**compound 61**) (2.6 g, 98 %).

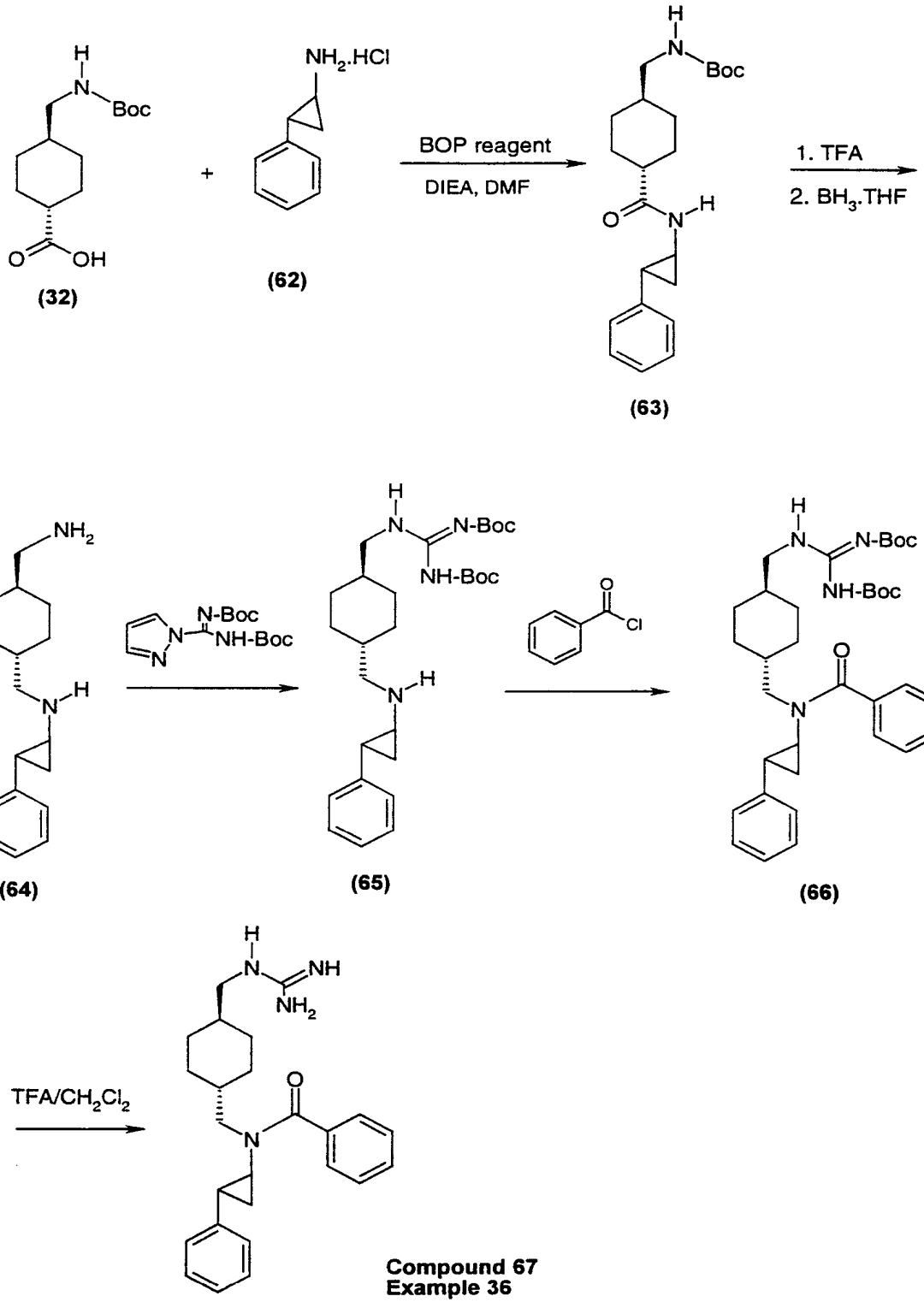
^{1}H NMR: ($CDCl_3$, TMS) δ **(ppm):** 7.35-7.22 (12H, m, Ar), 7.00-6.98 (3H, m, Ar), 4.60-4.58 (1H, m, C<u>H</u>), 4.16-4.14 (1H, m, C<u>H</u>$_2$N), 3.97 (1H, s, br, C<u>H</u>$_2$N), 3.36 (1H, s, br C<u>H</u>$_2$N), 2.82-2.80 (1H, m, C<u>H</u>$_2$N), 2.49 (2H, m, C<u>H</u>$_2$N), 1.81-1.53 (7H, m),1.09 (1H, m), 0.83-0.80 (2H, m), 0.59-0.55 (2H, m).

<u>Example 36</u>

<u>Preparation of *trans*-1-[N-(*trans*-2-phenyl cyclopropyl)-N-benzoyl]-aminomethyl -4-guanidinomethyl cyclohexane (compound 67)</u>

Compound 67 of this Example was prepared by following the synthetic route described in **Scheme 7** below.

Scheme 7



Compound 67
Example 36

Step 1

Preparation of *trans*-4-N-(Boc)-aminomethyl cyclohexane-1-(*trans*-2-phenyl cyclopropyl) carboxamide (compound 63)

The **compound 63** was prepared according to the general protocol for amide bond formation: To an ice-cooled DMF solution (15 mL) of *trans*-2-phenylcyclopropylamine hydrochloride (**compound 62**) (0.848 g, 5 mmol) was added DIEA (3.071 mL, 17.5 mmol), *trans*-4-N-(Boc)aminomethyl cyclohexane carboxylic acid (**compound 32**) (1.285 g, 5 mmol), and BOP reagent (2.21 g, 5 mmol). The reaction mixture was stirred at r.t. overnight and worked up according to the general protocol.

Step 2

Preparation of *trans*-4-aminomethyl -1-N-(*trans*-2-phenyl cyclopropyl)-aminomethyl cyclohexane (compound 64)

trans-4-N-(Boc)-aminomethyl cyclohexane-1-(*trans*-2-phenyl cyclopropyl)carboxamide (**compound 63**) prepared in the previous step 1 (1.1 g, mmol) in 50%TFA/CH_2Cl_2 was stirred at r.t. for 1.5 h and then concentrated. The crude product was diluted with methylene chloride and neutralized with K_2CO_3 solution. The organic layer containing the carboxamide was dried over $MgSO_4$ and concentrated to a solid residue:

MS(APCI): 273.1 (M+H).

The carboxamide (0.200 g. 0.7 mmol) was suspended in THF (3 mL). A 1 M solution of borane.THF complex (6 mL) was added and the reaction mixture was refluxed overnight. After cooling to r.t. a 1.77 M solution of HCl in methanol (3.3 mL) was added, and the mixture was heated at reflux for 2 h. Excess reagent and solvent were removed under reduced pressure. The residue was dissolved in CH_2Cl_2 and washed with 1 N NaOH, brine, dried over $MgSO_4$ and concentrated: 0.184 g.

MS(APCI): 259.1 (M+H)

Step 3

Preparation of *trans*-4-N-(diBoc)-guanidinomethyl -1-N-(*trans*-2-phenyl cyclopropyl)-aminomethyl cyclohexane (compound 65)

The crude diamine (**compound 64**) (0.18 g) was reacted with an equimolar 1-H-pyrazole-1-(N,N-*bis*(tert-butoxycarbonyl)-carboxamidine in THF following the protocol described in the General Procedure. The product was purified by silica gel chromatography: 0.059 g.

MS(APCI): 501.2 (M+H), 401.2, 301.2

Step 4

Preparation of *trans*-4-N-(diBoc)-guanidinomethyl -1-[N-(*trans*-2-phenyl cyclopropyl)-N-benzoyl]-aminomethyl cyclohexane (compound 66)

Benzoylation was carried out according to the protocol described in the General Procedure. The product was purified by preparative TLC using a mixture of ethyl acetate/hexane as the eluent: 0.026 g.

MS(APCI): 605.1 (M+H), 505.2, 405.1

Step 5

Preparation of *trans*-1-[N-(*trans*-2-phenyl cyclopropyl)-N-benzoyl]aminomethyl -4-guanidinomethyl cyclohexane (compound 67)

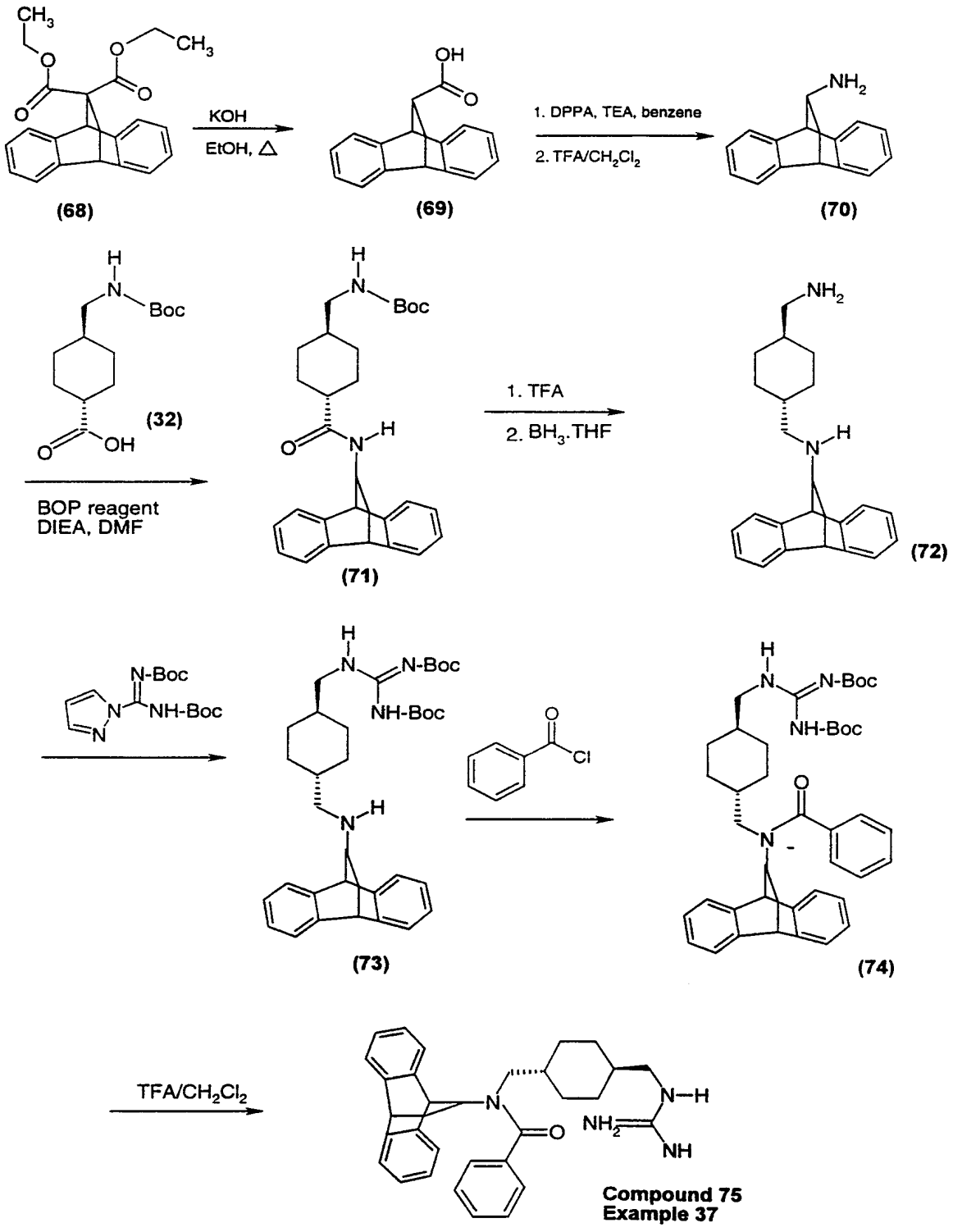
The deprotection was carried out according to the protocol described in the General Procedure. Solvent and excess reagent were removed under reduced pressure. The residue was dissolved in a mixture of acetonitrile/water and lyophilized to give the product as a powder:

MS (APCI): 405.2 (M+H)

Example 37

The **compound 75** of Example 37 was prepared by following the synthetic procedure described in **Scheme 8** below.

Scheme 8


KOH
EtOH, △
1. DPPA, TEA, benzene
2. TFA/CH2Cl2
(68)
(69)
(70)
(32)
BOP reagent
DIEA, DMF
(71)
1. TFA
2. BH3.THF
(72)
(73)
(74)
TFA/CH2Cl2
Compound 75
Example 37

Step1

Preparation of 9,10-Dihydro-9,10-ethanoanthracene-11-carboxylic acid (compound 69)

Diethyl 9,10-Dihydro-9,10-ethanoanthracene-11,11-dicarboxylic acid (2.05 g, 5.85 mmol) was dissolved in a 95% ethanolic aqueous solution. KOH pellets (0.794 g) were added and the mixture was refluxed overnight. The reaction mixture was extracted with diethyl ether. The ether extracts were concentrated to give a solid residue (**compound 69**) which was fractionated on a silica gel column to give the product (0.84 g):

^{1}H NMR ($CDCl_3$) δ 7.05-7.40 (m, 8H), 4.67 (m, 1H), 4.32 (m, 1H), 2.90 (m, 1H), 1.96-2.18 (m, 2H). MS(APCI) -Q1MS: 249.0 (M-H).

Step 2

Preparation of 9,10-Dihydro-9,10-ethanoanthracene-11-amine (compound 70)

A round bottom flask was charged with 9,10-Dihydro-9,10-ethanoanthracene-11-carboxylic acid (0.635 g, 2.54 mmol), benzene (10 mL), triethylamine (0.356 mL), and diphenylphosphoryl azide (0.718 g). The solution was heated at 90 C for 1 h. t-Butanol (0.222 g) was added to the reaction mixture and it was refluxed overnight. The reaction mixture was then concentrated, redissolved in ethyl acetate, washed with sodium bicarbonate, brine, dried over Mg SO_4 and concentrated. Brief exposure to 50%TFA/CH_2Cl_2, followed by neutralization with potassium carbonate solution gave the amine:

^{1}H NMR ($CDCl_3$) δ 7.20 (m, 8H), 4.38 (br s, 1H), 4.26 (br s, 1H), 3.75 (m, 1H), 2.32 (m, 1H), 1.55 (m, 1H), 1.50 (s, 2H). MS(APCI): 222.1 (M+H)

Step 3

Preparation of *trans*-4-N-(Boc)-aminomethyl cyclohexane-1-N-(9,10-dihydro-9,10-ethanoanthracen-11-yl)-carboxamide (compound 71)

This compound was prepared according to the General Procedure described for amide formation: To an ice-cooled DMF solution (5 mL) of 9,10-Dihydro-9,10-ethanoanthracene-11-amine (0.221 g, 1 mmol) was added DIEA (0.479 mL, 2.75 mmol),

trans-4-N-(Boc)aminomethyl cyclohexane carboxylic acid (0.282 g, 1.1 mmol), and BOP reagent (0.487 g, 1.1 mmol). The reaction mixture was stirred at r.t. overnight and worked up according to the general protocol. **Crude yield**: 0.418 g. The product was purified by silica gel chromatography.

Step 4

Preparation of *trans*-4-aminomethyl -1-N-(9,10-dihydro-9,10-ethanoanthracen-11-yl)aminomethyl cyclohexane (compound 72)

trans-4-N-(Boc)-aminomethyl cyclohexane-1-N-(9,10-dihydro-9,10-ethanoanthracen-11-yl)carboxamide (0.28 g, 0.61mmol) in 50%TFA/CH_2Cl_2 was stirred at r.t. for 1.5 h and then concentrated. The crude product was diluted with methylene chloride and neutralized with K_2CO_3 solution. The organic layer was dried over $MgSO_4$ and concentrated to a solid residue:

^{1}H NMR ($CDCl_3$) δ 7.20 (m, 8H), 4.84 (br d, 1H), 4.36 (m, 2H), 4.28 (br s, 1H), 2.50 (d, 2H), 2.35 (m, 1H), 1.8 (m, 5H), 1.2-1.5 (m, 4H), 0.85 (m, 2H).

MS(APCI): 361.1 (M+H)

The carboxamide (0.22 g, .61 mmol) was dissolved in THF (3 mL). A 1 M solution of borane.THF complex (2.5 mL) was added and the reaction mixture was refluxed overnight. After cooling a 1.77 M solution of HCl in methanol (1.4 mL) was added, and the mixture was heated at reflux for 2 h. Excess reagent and solvent were removed under reduced pressure. The residue was dissolved in CH_2Cl_2 and washed with 1 N NaOH, brine, dried over $MgSO_4$ and conconetrated: 0.165 g.

MS(APCI): 347.2 (M+H)

Step5

Preparation of *trans*-4-N-(diBoc)-guanidinomethyl -1-N-(9,10-dihydro-9,10-ethanoanthracen-11-yl)-aminomethyl cyclohexane (compound 73)

The crude diamine (0.16 g, 0.46mmol) was reacted with an equimolar 1-H-pyrazole-1-(N,N-*bis*(tert-butoxycarbonyl)-carboxamidine in THF. The product was purified by silica gel chromatography: 0.290 g.

MS(APCI): 589.2(M+H), 489.2, 389.1

Step 6

Preparation of *trans*-4-N-(diBoc)-guanidinomethyl -1-[N-(9,10-dihydro-9,10-ethanoanthracen-11-yl)-N-benzoyl]aminomethyl cyclohexane (compound 74)

Benzoylation was carried out according to the protocol described in the General Procedure. The product was purified by preparative TLC using a mixture of ethyl acetate/hexane as the eluent: 0.174 g.

MS(APCI): 693.2 (M+H), 593.1, 493.1

Step 7

Preparation of *trans*-1-[N-benzoyl-N-(9,10-dihydro-9,10-ethanoanthracen-11-yl)]aminomethyl -4-guanidinomethyl cyclohexane (compound 75)

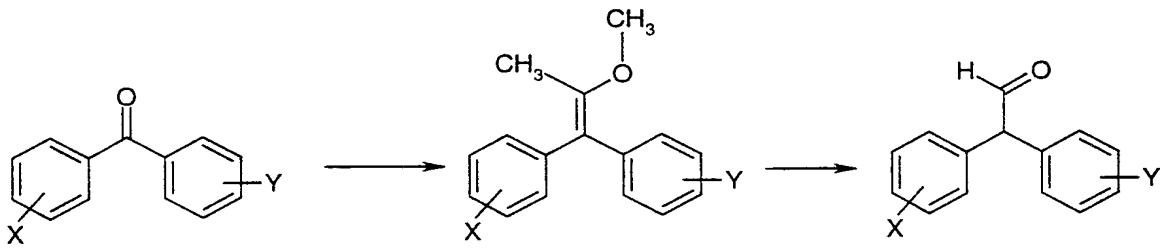
The deprotection was carried out according to the protocol described in the General Procedure. Solvent and excess reagent were removed under reduced pressure. The residue was dissolved in a mixture of acetonitrile/water and lyophilized to give the product as a powder:

MS (APCI): 493.15 (M+H)

General Procedures for the preparation of substituted diphenylethyl derived compounds:

Substituted diaryl acetaldehyde may be prepared according to the following reaction **Scheme 9**, that is, by a Wittig reaction on the corresponding diaryl ketone to form an enol ether which was then hydrolyzed to the aldehyde by acid treatment.

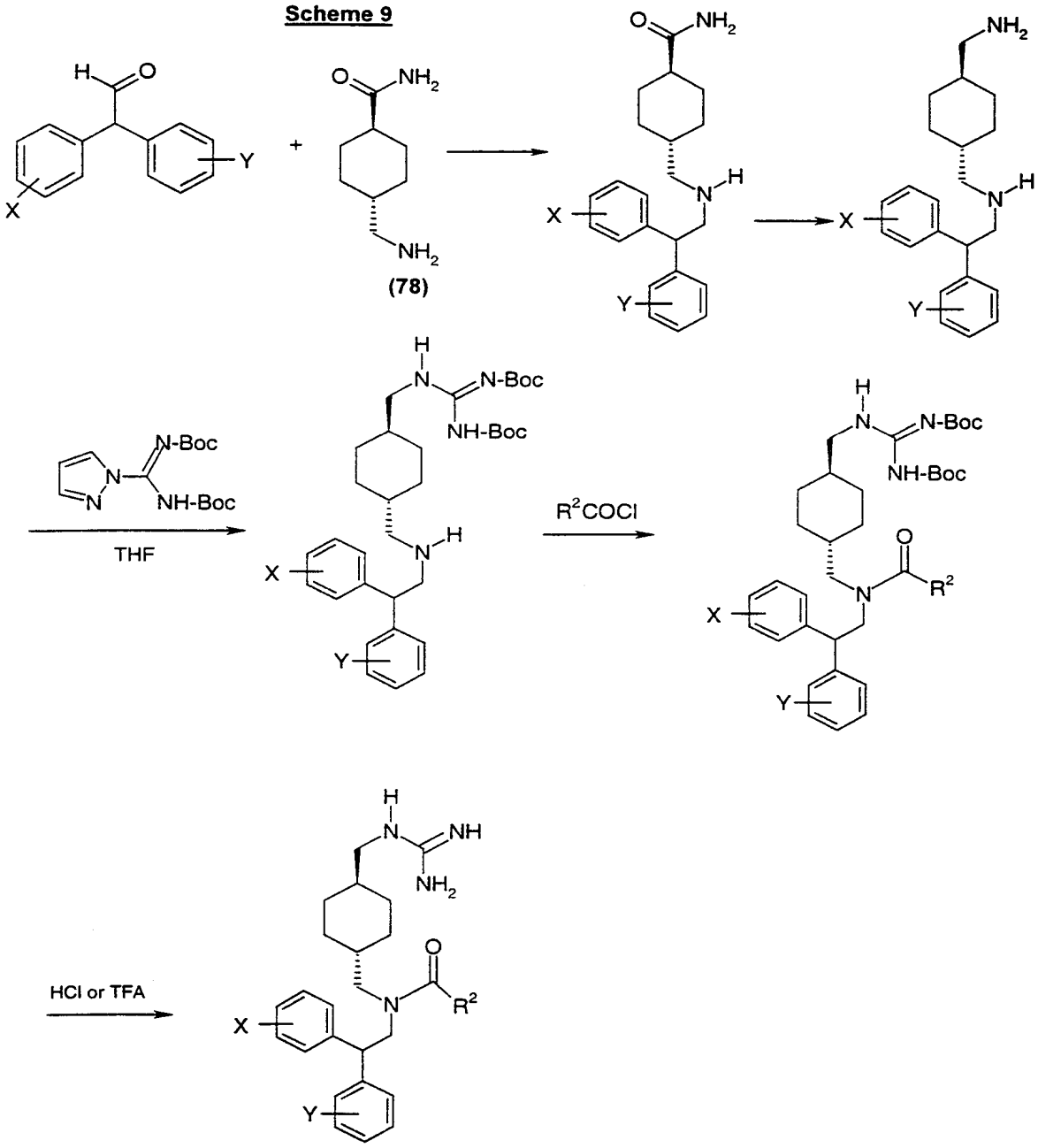
Scheme V



(XXIII) (XXIV) (XXV)

The substituted diaryl acetaldehyde was then reacted with *trans*-4-aminomethyl cyclohexane carboxamide under reductive amination conditions to form the secondary amine. The carboxamide was then reduced by borane to the primary amine which was guanylated. The secondary amine was then acylated, and finally the protecting group was removed by acid treatment to release the free guanidine. The reaction sequence is depicted in Scheme 9 below:

Scheme 9

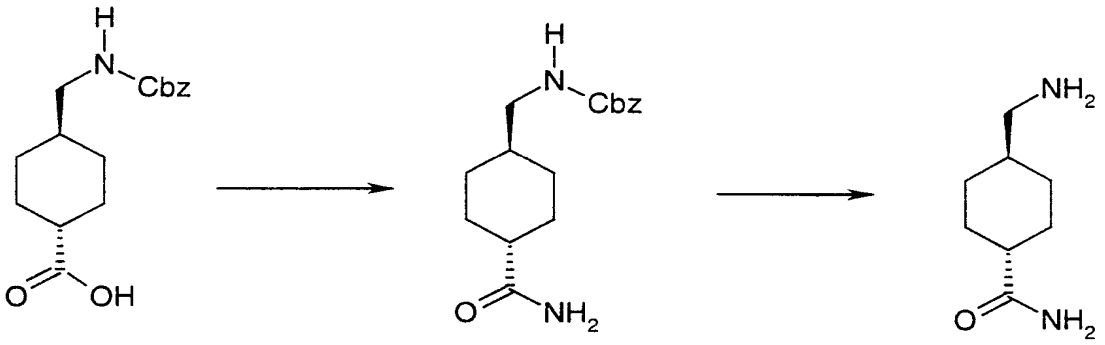


Examples 39-47
Compounds 79-88

Step 1

Preparation of *trans*-1-carboxamide-4-aminomethyl cyclohexane (compound 78)

Scheme 10



To an ice-cooled THF solution (300 mL) containing *trans*-1-N-Cbz-aminomethyl-cyclohexane-4-carboxylic acid (29.1 g, 0.1 mol) was added N-methylmorpholine (11 mL, 0.1 mol) and isobutyl chloroformate (13 mL, 0.1 mol). After 4 minutes, a 30% solution of ammonium hydroxide (30mL, 0.53 mol) was added. The reaction mixture was agitated while the reaction was allowed to warm to r.t. in one hour. The reaction mixture was duluted with ethyl acetate and the precipitated product was collected by filtration. The solid residue was washed with aq. sodium bicarbonate, water, and dried, 25.1 g (98%).

^{1}H NMR (DMSO-d$_6$) δ 7.12 (m, 5H), 7.0 (t, 1H), 6.9 (br s, 1H), 6.35 (br s, 1H), 4.77 (s, 2H), 2.65 (t, 2H), 1.75 (m, 1H),), 1.5 (m, 4H), 1.0 (m, 3H), 0.6 (m, 2H). MS(APCI): 291.05 (M+H).

The Cbz-protected *trans*-1-N-Cbz-aminomethyl cyclohexane-4-carboxamide (25.1 g, 98 mmol) was dissolved in a mixture of methanol (200 mL) and DMF (40 mL). The solution was hydrogenolyzed at 50 psi in the presence of a 10% Pd/C catalyst (3.5 g). The reaction mixture was filtered through a pad of Celite. The filtrate was evaporated to give a solid, 15.2 g.

^{1}H NMR (DMSO-d6) δ 7.15 (s, 1H), 6.6 (s, 1H), 4.3 (br s, 2H), 2.35 (d, 2H), 1.9 (m, 1H), 1.7 (m, 4H), 1.25 (m, 3H), 0.8 (m, 2H).

MS(APCI): 157.05 (M+H).

Step 2

Enol ether formation (general formula XXIV)

To a suspension of the methoxymethyl triphenylphosphine chloride (2 eq) in anhydrous THF was added potassium tert-butoxide (2 eq) (alternatively sodium hydride can be used). To this solution was added a THF solution containing diaryl ketone (1 eq) of the general formula XXIII. The reaction mixture was stirred under nitrogen or argon overnight, at r.t. or warmed to 70° C if necessary. Water was added, and the reaction mixture was diluted with ethyl acetate and aq. sodium bicarbonate. The organic layer was washed with brine, dried over MgSO4 and concentrated. The product was purified by silica gel chromatography using a mixture of ethyl acetate and hexane as the eluent.

Step 3

Conversion of enol ether to aldehyde (general formula XXV)

The enol ether of the general formula XXIV(1 eq) and p-toluenesulfonic acid monohydrate (5 eq) (aq. HCl may be used) was dissolved in THF. The mixture was heated at reflux for up to 16 h. and then was diluted with diethyl ether, washed with water, aq. sodium bicarbonate, brine, dried over $MgSO_4$ and concentrated. The product aldehyde of the general formula XXV may be purified by silica gel chromatography.

Step 4

Preparation of secondary amines by reductive amination

To a solution of *trans*-1-aminomethyl cyclohexane-4-carboxamide (**compound 78**)(1 eq) in methanol containing 1% (v/v) of glacial acetic acid (alternatively, $ZnCl_2$ can be used) was added aldehyde (1 eq), followed by $NaBH_3CN$ (3-4 eq). The reaction mixture was stirred at room temperature overnight. The reaction was quenched with water, basified with aqueous $NaHCO_3$ solution and extracted with methylene chloride. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was

chromatographed on silica gel using a mixture of methylene chloride/methanol as the eluent.

Step 5

Reduction of carboxamide

The carboxamide product (1 eq) from above was dissolved in minimum amount of THF. To this solution was added a 1M solution of BH_3.THF complex (3-5 molar excess) and the reaction mixture was heated at reflux overnight. After cooling to r.t., a methanolic hydrochloric acid solution (3-5 molar excess) was added to the reaction mixture and the mixture was refluxed for 2-4 h. It was then concentrated, diluted with methylene chloride and washed with N NaOH, brine, dried over $MgSO_4$ and concentrated.

Step 6

Guanylation

The above product diamine (1 eq) was dissolved in THF and 1-H-pyrazole-1-(N,N-*bis*(tert-butoxycarbonyl)carboxamidine (1 eq) was added. The mixture was stirred at r.t. for 2-3 h and then concentrated. The product was purified by silica gel chromatography using ethyl acetate/hexane or methylene chloride/methanol as the eluent.

Step 7

Acylation

To a solution of secondary amine (1 eq) in dioxane or methylene chloride was added triethylamine (1.5-2.0 eq), followed by the acid chloride (1 eq). The reaction mixture was stirred at room temperature for 3 h-overnight, then basified with 1N K_2CO_3 solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, concentrated and chromatographed on silica gel or purified by preparative TLC using a mixture of hexane-ethyl acetate as the eluent.

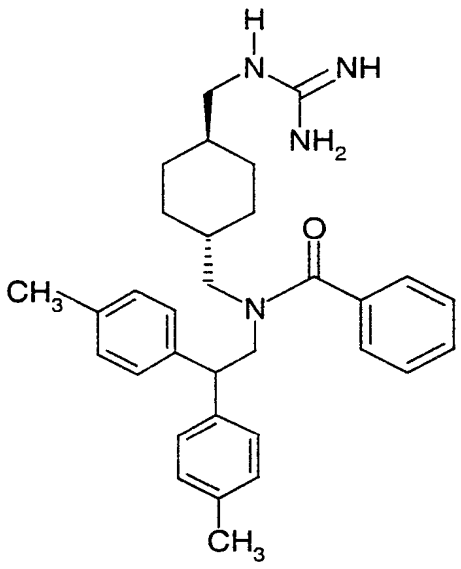
Step 8

Deprotection of diBoc-guanidino compounds

The diBoc-guanidino compound was dissolved in 4N HCl in dioxane or 50% trifluoroacetic acid in methylene chloride and stirred at room temperature for 2 h to overnight. The solvent was removed under reduced pressure. The residue was dissolved in water and lyophylized. The product can also (when appropriate) be purified by reversed-phase HPLC using acetonitrile-water as the eluent.

Example 38

Preparation of *trans*-1-[(N-Benzoyl) -N-(2,2'-Di(p-Tolyl)ethyl)]-aminomethyl-4-guanidinomethyl cyclohexane hydrochloride (compound 79)



Compound 79

Following the procedure described in the general procedures for the preparation of substituted diphenylethyl derived compounds step 2, but using 4,4-dimethylbenzophenone as the dialkyl ketone followed by step 3 to 8, the title **compound 79** was achieved.

^{1}H NMR (MeOD-d_4) δ 7.35 (m, 4H), 7.3 (d, 2H), 7.15 (d, 2H), 7.05 (m, 4H), 6.90 (d, 1H), 4.55 (t, 1H), 4.15 (d, 2H), 3.05 (dd, 2H), 2.85 (d, 2H), 2.6 (s, 6H), 1.9 - 1.75 (m, 4H), 1.0 (m, 4H), 0.6 (m, 2H).

MS(APCI):497.53

Examples 39-45

By following the same synthetic procedure as described for the preparation of compound 79 of Example 38, the compounds indicated in Table 3 below were prepared.

Table 3

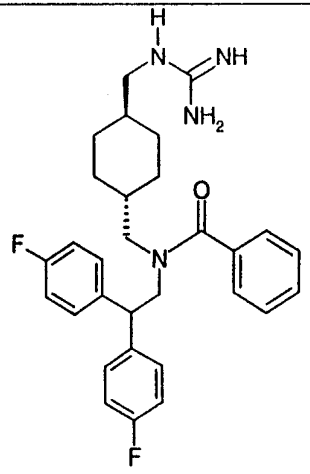
Ex	Structure	Chemical name	Diaryl ketone	Physical Characterization
39	 Compound 80	Trans-1-[N-(benzoyl)-N-(4,4'-difluorodiphenylethyl)]-aminomethyl-4-guanidinomethyl cyclohexane	4,4-difluoro-benzophenone	**^{1}H NMR (DMSO-d_6)** δ 8.1-6.51 (m, 13H), 4.50 (broad t, 1H), 4.2-3.65 (m, 3H), 2.95-2.53 (m, 4H), 1.78-0.20 (m, 10H). **MS:** 505.4 (M+H).

Table 3 (contd.)

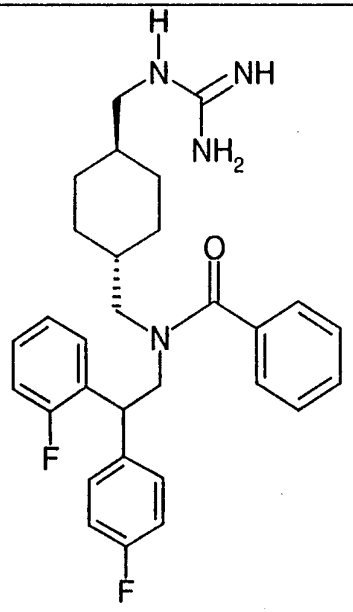
Ex	Structure	Chemical name	Diaryl ketone	Physical Characterization
40	 **Compound 81**	Trans-1-[N-(Benzoyl)-N-(2,4'-difluorodiphenylethyl)]-aminomethyl-4-guanidinomethyl cyclohexane	2,4´-difluoro-benzophenone	**^{1}H NMR (DMSO-d$_6$)** δ 8.1-6.49 (m, 13H), 4.90-2.68 (m, 7H), 1.85-0.30 (m, 10H). **MS:** 505.36 (M+H).

Table 3 (Contd.)

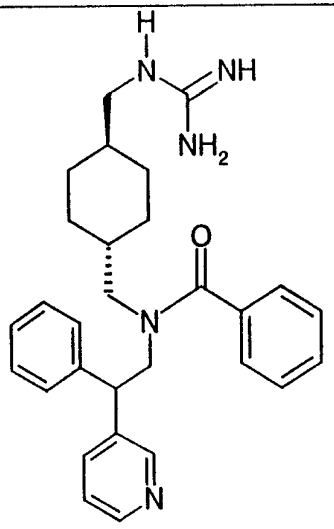
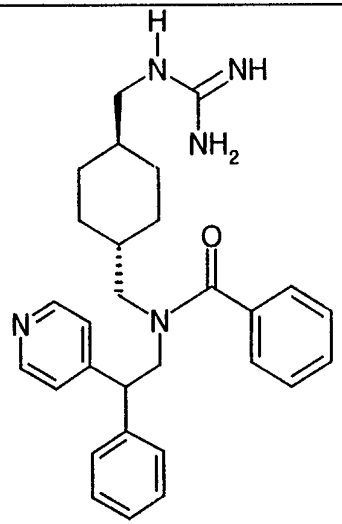
Ex	Structure	Chemical name	Diaryl ketone	Physical Characterization
41	 **Compound 82**	Trans-1-[N-(benzoyl)-N-(2-phenyl-2-(3'-Pyridyl)Ethyl)]-aminomethyl-4-guanidinomethyl cyclohexane	3-benzoyl pyridine	**^{1}H NMR (DMSO-d$_6$)** δ 8.86 (s, 1H), 8.65 (s, 1H), 8.48 (broad d, 1H), 8.25 (d, 1H), 7.72-6.6 (m, 14H), 4.7 (broad t, 1H), 4.33.95 (m, 2H), 3.32-2.74 (m, 4H), 1.80-0.32 (m, 10H). **MS:** 470.4 (M+H).

Table 3 (Contd.)

Ex	Structure	Chemical name	Diaryl ketone	Physical Characterization
42	 **Compound 83**	Trans-1-[N-(benzoyl)-N-(2-phenyl-2-(4-pyridyl)ethyl)]-aminomethyl-4-guanidinomethyl cyclohexane dihydrochloride	4-benzoyl pyridine	**^{1}H NMR (MeOD-d$_4$)** δ 8.85 (broad s, 2H), 8.2 (broad s, 1H), 7.45 (m, 8H), 7.05 (d, 1H), 4.20 (broad, 1H), 3.5-3.8 (m, 4H), 2.95 (broad s, 2H), 0.6-1.9 (m, 10H). **MS(APCI):** 470.4

Ex	Structure	Chemical name	Diaryl ketone	Physical Characterization
43	Compound 84	Trans-1-[N-(benzoyl)-N-(2-(1-naphthyl)-2-phenylethyl]-aminomethyl]-4-guanidinomethyl cyclohexane	1-benzoyl naphtalene	MS(APCI): 519.2

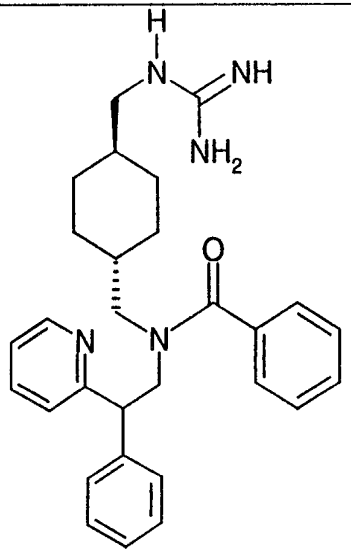
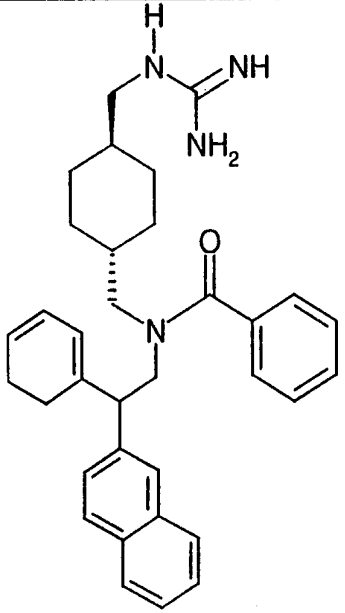
Ex	Structure	Chemical name	Diaryl ketone	Physical Characterization
44	 **Compound 85**	Trans-1-[N-(benzoyl)-N-(2-phenyl-2-(2-pyridyl))-ethyl]-aminomethyl-4-guanidinomethyl cyclohexane	2-benzoyl pyridine	**^{1}H-NMR (MeOD-d_4)** δ 8.65 (s, 1H), 8.5 (s, 1H), 8.0 (broad s,1H), 7.80 (t, 1H), 7.65 (d, 1H), 7.38 (m, 6H), 7.20 (d, 1H), 7.1(d, 1H), 7.00 (d, 1H), 4.15-4.45 (m, 3H), 3.03 (m, 2H), 2.85 (m, 2H), 1.9 - 0.75 (m, 10H). **MS(APCI):** 470.1

Table 3 (Contd.)

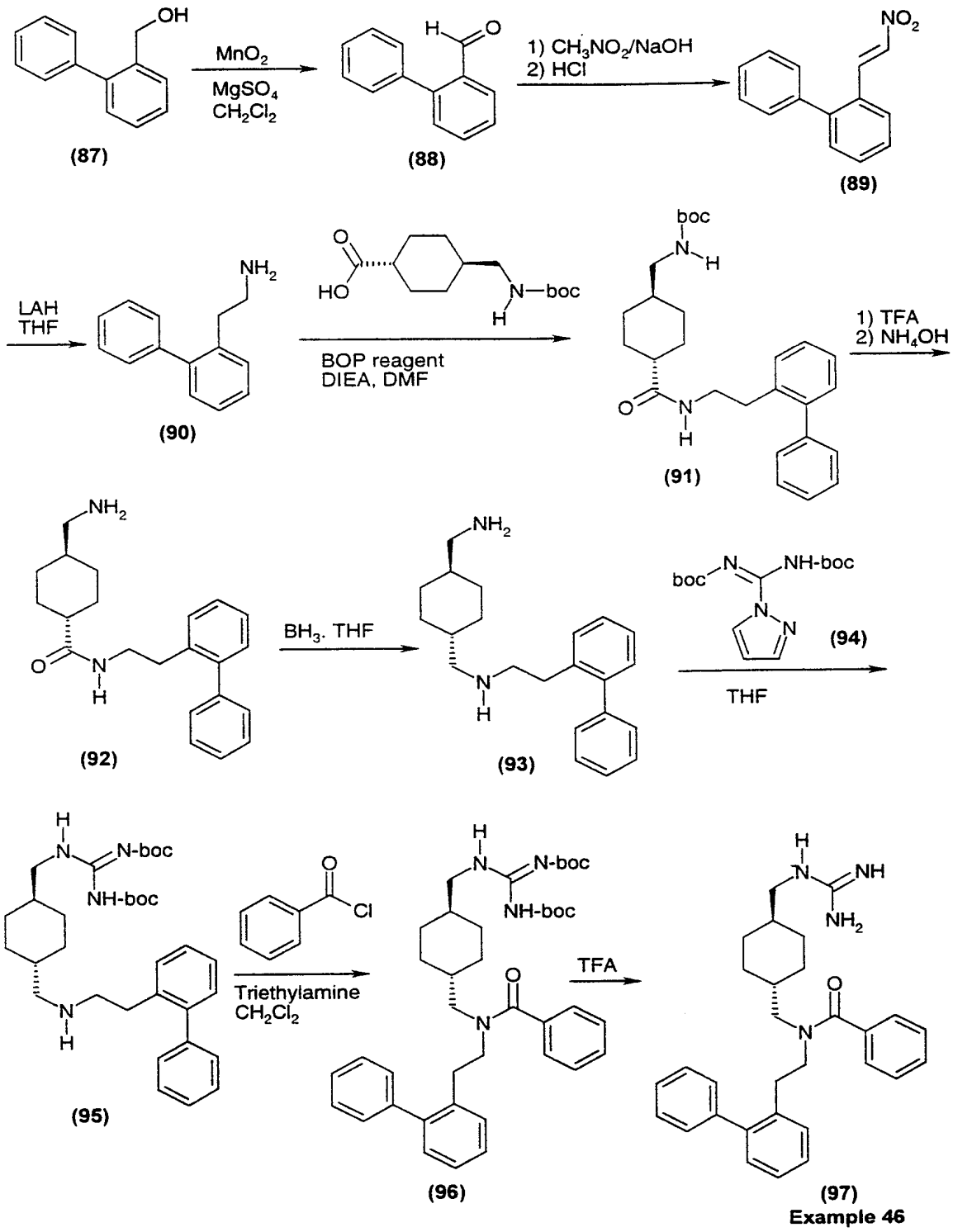
Ex	Structure	Chemical name	Diaryl ketone	Physical Characterization
45	 **Compound 86**	Trans-1-[N-(benzoyl) -N-(2-(phenyl)-2-(2-naphthyl)-ethyl]-aminomethyl-4-guanidinomethyl cyclohexane	2-benzoyl naphtalene	**MS**: 519.1 (M+H).

Example 46

Preparation of Trans-1-[N-(benzoyl)-N-(2-phenyl-2-phenylethyl)]-aminomethyl-4-guanidinomethyl cyclohexane hydrochloride (compound 97)

The **compound 97** of this Example, was prepared by following the synthetic route described in **Scheme 11** below.

Scheme 11


OH
MnO2
MgSO4
CH2Cl2
H
O
1) CH3NO2/NaOH
2) HCl
NO2
(87)
(88)
(89)
LAH
THF
NH2
HO
O
N—boc
H
BOP reagent
DIEA, DMF
boc
N
H
1) TFA
2) NH4OH
(90)
(91)
NH2
BH3. THF
boc
N
NH-boc
(94)
THF
(92)
(93)
N-boc
NH-boc
Cl
Triethylamine
CH2Cl2
TFA
NH
NH2
(95)
(96)
(97)
Example 46

Step 1

Preparation of 2-Phenyl benzaldehyde (compound 88)

To a solution of **compound 87** (10.6 g, 57.6 mmol) in methylene chloride (250 mL) was added manganese dioxide (63.16 g), and anhydrous magnesium sulfate (15 g). The mixture was stirred at r.t. for 16 h. The black suspension was filtered and washed with 4x100 mL of methylene chloride, concentrated in vacuo to give an almost colorless and highly refractive liquid **(compound 88)** (9.81 g): DNPH active, single spot on TLC (R_f 0.39 in 4/1 hexane:ethyl acetate).

Step 2

Preparation of 2-Phenyl nitrostyrene (compound 89)

Compound 89 was synthesized in a similar fashion as reported for nitrostyrene (Organic Syntheses, Coll. Vol. I, 2nd ed., John Wiley & Sons, 1941, p.413): In a 1 litre round bottom flask placed in an ice bath and containing a solution of the aldehyde **(compound 88)** (9.81 g, 53.8 mmol) and nitromethane (3.3 g, 54.0 mmol) in methanol (25 mL) was added dropwise in 10 minutes a solution of 2.27 g NaOH in 3 mL of water. A viscous and almost colorless clear solution formed. This reaction mixture was stirred in the cold bath for 4.5 h. Then the light brownish clear solution was added dropwise to 20 mL of well stirred hydrochloric acid solution (1.5:1/water:conc. HCl) in 15 minutes. A bright yellowish brown oil formed. After about half of the reaction mixture was added, additional conc. HCl (10 mL) was added to the acidic solution and addition of the nitronate was continued. A thick brown oil formed. The mixture was stirred at r.t. for 1.5 h, then was extracted with methylene chloride 3 times. The organic extracts were combined, dried over magnesium sulfate and concentrated. The crude was chromatographed on silica gel column and eluted with a mixture of 20:1 hexane:ethylacetate. The nitroolefin product **(compound 89)** was recrystallized from diethyl ether-hexane: 4.8 g of lemon yellow needles.

Step 3

Preparation of 2-Phenyl-2-phenethylamine (compound 90)

Compound 90 was synthesized in a similar fashion as reported in the literature (A. Kubo et al, Synthesis, 824 (1987)): In a 500 mL round bottom flask was placed LAH (2.5 g, 65.88 mmol) and dry THF (100 mL). To the stirred LAH suspension was added dropwise a solution of the nitroolefin **(compound 89)** (3.9 g, 17.33 mmol) in THF (10 mL) in 20 minutes. An exothermic reaction occurred. The reaction mixture was stirred for 15 minutes at r.t., then was heated to just boil for 10 minutes, and then was stirred at r.t. for 48 h. It was then cooled to 0°C and decomposed with 30% NaOH, diluted with hexane (20 mL), diethyl ether (100 mL) and allowed to warm to r.t. The mixture was dried with potassium carbonate, filtered, and concentrated to an oil.

MS (APCI): 198. (M+H).

Step 4

Preparation of Trans-1-(2-Phenyl-2-phenethyl)-4-N-Boc-4-aminomethyl cyclohexane carboxamide (compound 91)

To an ice-cooled DMF solution (5 mL) of *trans*-N-Boc-4-aminomethyl cyclohexane carboxylate (0.257 g, 1 mmol) was added 2-phenyl phenethylamine **(compound 90)** (0.197 g, 1 mmol), diisopropylethylamine (0.435 mL, 2.5 mmol) and BOP reagent (0.442 g, 1 mmol) successively. The reaction mixture was stirred overnight at r.t. It was then diluted with ethyl acetate and washed with water, 1% HCl, sodium bicarbonate solution, brine and dried over magnesium sulfate and then concentrated. The product **(compound 91)** was purified on a silica gel column (eluting solvent : methylene chloride to 3% methanol in methylene chloride): 0.35 g.

MS(APCI): 437.2 (M+H).

Step 5

Preparation of Trans-(2-Phenyl-2-phenethyl)-4-aminomethyl cyclohexane carboxamide (compound 92)

Compound **91** (0.34 g, 0.78 mmol) was dissolved in 50% trifluoroacetic acid in methylene chloride (5 mL) and stirred at r.t. for 2 h. The reaction mixture was concentrated and then redissolved in methylene chloride, basified with 30% ammonium hydroxide. The organic layer was washed with brine, dried over magnesium sulfate and then concentrated to a syrupy residue **(compound 92):**

MS (APCI) 336.90 (M+H).

Step 6

Preparation of *trans*-1-N-(2-phenyl-2-phenethyl)-aminomethyl-4-aminomethyl cyclohexane (compound 93)

Compound 92 (0.191 g, .57 mmol) was dissolved in dry THF (2 mL). To this solution was added a 1 M solution of borane.THF complex (1.7 mL) and the reaction mixture was heated at reflux for 16 h under nitrogen. After cooling to r.t., a 3.3 M solution of HCl in methanol (0.7 mL) was added to the reaction mixture and the mixture was refluxed for 2 h. After cooling to r.t., the reaction mixture was concentrated and then basified with 1N NaOH. The product was extracted with methylene chloride. The organic extractes were dried over magnesium sulfate and concentrated to give **(compound 93):**

MS (APCI) 323.16 (M+H).

Step 7

Preparation of *trans*-1-N-(2-phenyl-2-phenethyl)-aminomethyl-4-N-(diBoc)-guanidinomethyl cyclohexane (compound 95)

The diamine (**compound 93**) (0.18 g, .56 mmol) was dissolved in THF (5 mL). To this solution was added diBOC-guanylpyrazole **(compound 94)** (0.174 g, 0.56 mmol). The mixture was stirred at r.t. overnight, then was concentrated. The product (**compound 95)** was purified by silica gel chromatography (eluting solvent: methylene chloride to 3 % methanol in methylene chloride): 0.121 g.

^{1}H NMR ($CDCl_3$) δ 8.2 (br t, 1H), 7.05-7.3 (m, 10H), 3.08 (br t, 2H), 2.65 (t, 2H), 2.5 (t, 2H), 2.15 (d, 2H), 1.45-1.7 (m, 4H), 1.39 (s, 18H), 0.6-1.19 (m, 6H). MS (APCI): 565.37 (M+H).

Step 8

Preparation of Trans -1-[N-benzoyl-N-(2-phenyl-2-phenylethyl)]-aminomethyl-4-N-(diBoc)-guanidinomethyl cyclohexane (compound 96)

The acylation was carried out according to the General procedure for acylation of secondary amine: **Compound 95** (0.121 g, 0.214 mmol) was dissolved in methylene chloride (3 mL). To this solution was added triethylamine (0.060 mL, 0.429 mmol) and benzoyl chloride (0.028 mL, 0.24 mmol). The mixture was stirred at r.t. for 2 h. The product (**compound 96**) was purified by prep TLC (2mm thickness, solvent: 1:3/ethyl acetate: hexane): .118 g (83%).

Step 9

Preparation of *Trans*-1-[N-(benzoyl)-N-(2-phenyl-2-phenylethyl)]-aminomethyl-4-guanidinomethyl cyclohexane hydrochloride (compound 97)

The title **compound 97** (0.112 g, 0.167 mmol) was deprotected according to General procedure for deprotection of diBoc-guanidino compounds. The product (**compound 97**) was dissolved in an aqueous solution and lyophilized.

^{1}H NMR (DMSO-d6) δ 7.52-6.75 (m, 17H), 3.9 (m, 3H), 2.55-3.12 (m, 5H), 0.2-1.8 (m, 10H).

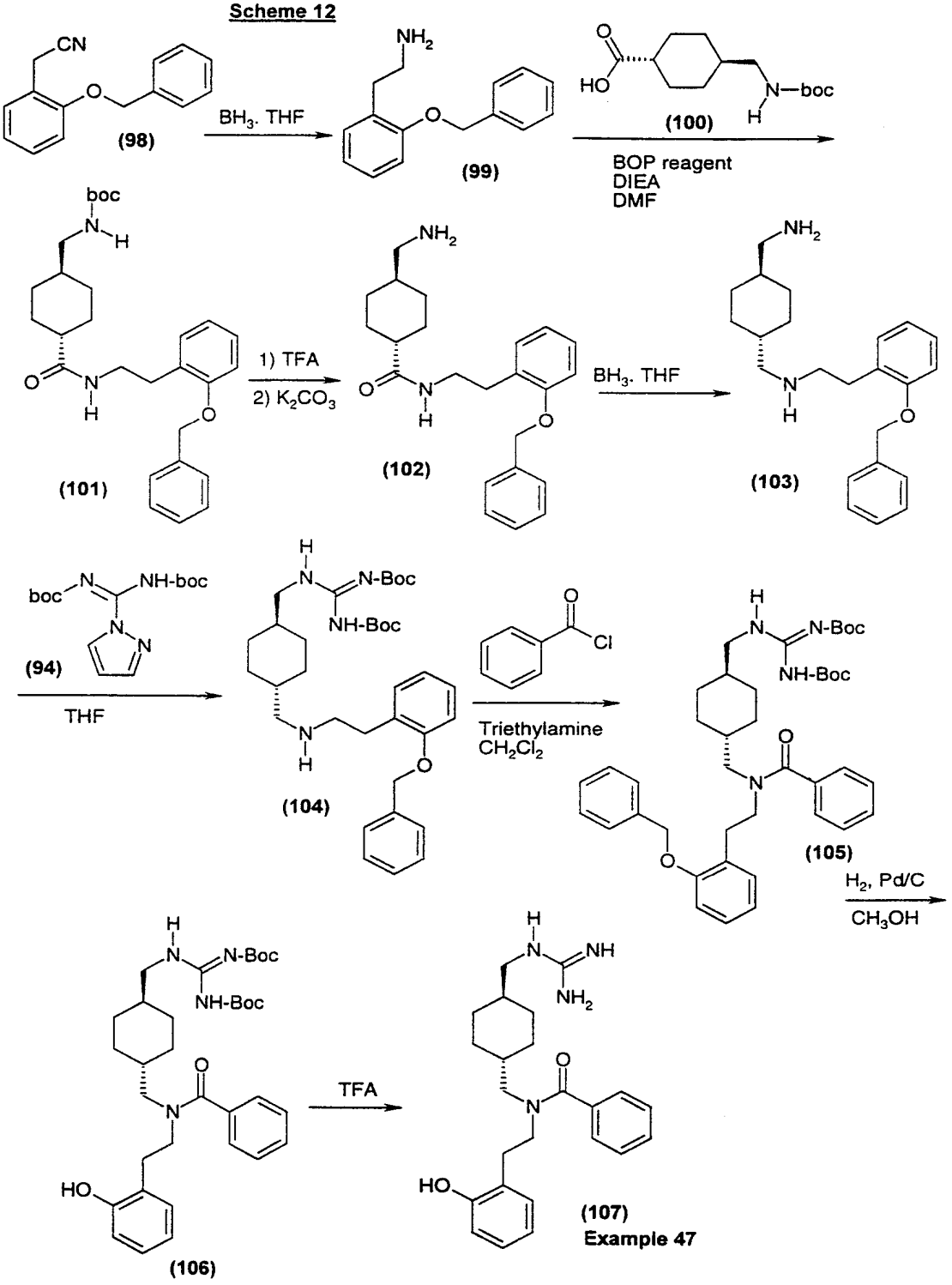
MS (APCI): 469.31 (M+H).

Example 47

Preparation of trans-[N-(benzoyl)-N-2-(2-hydroxyphenyl)ethyl]-aminomethyl-4-guanidinomethyl cyclohexane hydrochloride (compound 107)

The compound of this Example was prepared by following the synthetic procedure described in **Scheme 12** below.

Scheme 12


CN
(98)
BH3. THF
NH2
(99)
HO
N—boc
H
(100)
BOP reagent
DIEA
DMF
boc
(101)
1) TFA
2) K2CO3
(102)
BH3. THF
(103)
boc
NH-boc
(94)
THF
N-Boc
NH-Boc
(104)
Cl
Triethylamine
CH2Cl2
(105)
H2, Pd/C
CH3OH
(106)
TFA
NH
(107)
Example 47

Step 1

Preparation of 2-Benzyloxy-2- phenethylamine (compound 99)

2-benzyloxyphenylacetonitrile (**compound 98**) (15 g, 67.2 mmol) was dissolved dry THF (20 mL). To this solution was added a 1.0 M solution of borane/THF complex (200 mL). The reaction mixture was refluxed overnight, then cooled to r.t. A 3M solution of HCl in methanol.(67 mL) was added and the mixture was refluxed again for 3 h. After cooling, the reaction was basified with Na_2CO_3, extracted with methylene chloride, dried and concentrated to give **compound 99**.

MS:227.93 (M+H)

Step 2

Preparation of Trans-2-[(2-benzyloxyphenyl)ethyl]-N-Boc-4-aminomethyl cyclohexane carboxamide (compound 101)

Compound 99 (16 g)was dissolved in THF and cooled in an ice bath. *trans* -4-N-(Boc) aminomethyl cyclohexane-1-carboxylate (**compound 100**) (18.1 g) was added, followed by the additions of diisopropylethylamine (20 g), and BOP reagent (31 g). The reaction mixture was stirred at r.t. for 3 days. THF was removed and the reaction mixture was diluted with water and EtOAc. The organic layer was dried over magnesium sulfate and concentrated.The brown residue (**compound 101**)was repeatedly washed with ether until it was light yellow. **MS**: 466.93

Step 3

Preparation of Trans-2-[(2-benzyloxyphenyl)ethyl]-N-4-aminomethyl cyclohexane carboxamide (compound 102)

Compound 101 was deprotected by stirring in a 50% TFA/CH_2Cl_2 solution for 3 hours. Solvent and excess reagent were evaporated and the residue was redissolved in EtOAc and basified with K_2CO_3. At pH 9, white solid **(compound 102)** precipitated and was collected and washed with EtOAc and dried.

MS: 367.2

Step 4

Preparation of Trans-1-N-[2-(benzyloxyphenyl)ethyl]-aminomethyl-4-aminomethyl cyclohexane (compound 103)

Compound 102 (10 g) was dissolved in dry THF (10 mL) and a 1M solution of borane/THF complex (81 mL) was added.The reaction mixture was refluxed overnight, then cooled and a 2.8M solution of HCl in methanol (30 mL) was added.The mixture was refluxed again for 3 hours. After cooling to r.t., the reaction was basified with Na_2CO_3, extracted with methylene chloride, dried and concentrated. 7.6 g of product **(compound 103)** were obtained.

MS: 352.92

Step 5

Preparation of *trans*-1-N-[(2-Benzyloxyphenyl)ethyl]-aminomethyl-4-(diBoc)guanidinomethyl cyclohexane (compound 104)

Compound 103 (7.6 g) was reacted with diBoc-guanylpyrazole (**compound 94**) (6.7 g) in THF according to the conditions described in the general procedure to give the product (**compound 104**) (6.0 g).

MS: 595.23

Step 6

Preparation of Trans-1-[N-(benzoyl)-N-(2-benzyloxyphenyl)ethyl]-aminomethyl-4-(diBoc)guanidinomethyl cyclohexane (compound 105)

Compound 104 (6.0 g) was acylated with benzoyl chloride (1.68 g) according to the General procedure for acylation of secondary amine. The acylated product (**compound 105**) was purified by silica gel chromatography: 6.2 g.

^{1}H NMR ($CDCl_3$) δ 7.35 (m, 10H), 6.9 (broad, 4H), 5.70 (broad, 1H), 4.85 (s, 2H), 3.50 (t, 2H), 3.35(d, 2H), 3.15 (broad, 2H), 2.75(broad, 2H), 1.8 (m, 6H), 1.55 (s, 18H), 0.9 (m,4H). **MS**: 699.38

Step 7

Preparation of *trans*-1-[N-(benzoyl)-N-2-benzyloxyphenyl)ethyl]-aminomethyl-4-(diBoc)guanidinomethyl cyclohexane (compound 106)

Compound 105 (6.2 g) was dissolved in 5 ml of EtOAc and then diluted to 100 mL with methanol. 10% Pd on carbon catalyst (1 g) was added and the reaction was hydrogenolyzed (60 psi) in a Parr apparatus overnight. The reaction mixture was filtered through Celite and the filtrate was concentrated to give product (**compound 106**) (5 g).

^{1}H NMR ($CDCl_3$) δ 8.7 (broad, 1H), 8.3 (t, 1H), 7.5 (m, 5H), 7.25 (dd, 1H), 7.15 (d, 1H), 7.0 (d, 2H), 6.75 (dd, 1H), 3.60 (t, 2H), 3.25 (m, 4H), 3.0 (dd, 2H), 1.8 (m, 6H), 1.55 (s, 18H), 0.9 (m, 2H), 1.65 (m, 2H).

MS: 609.38

Step 8

Preparation of *trans*-1-[N-(benzoyl)-N-2-(2-hydroxyphenyl)ethyl]-aminomethyl-4-guanidinomethyl cyclohexane Hydrochloride (compound 107)

Compound 106 was deprotected according to the General procedure for deprotection of diBoc-guanidino compounds to give the free guanidino **compound 107** .

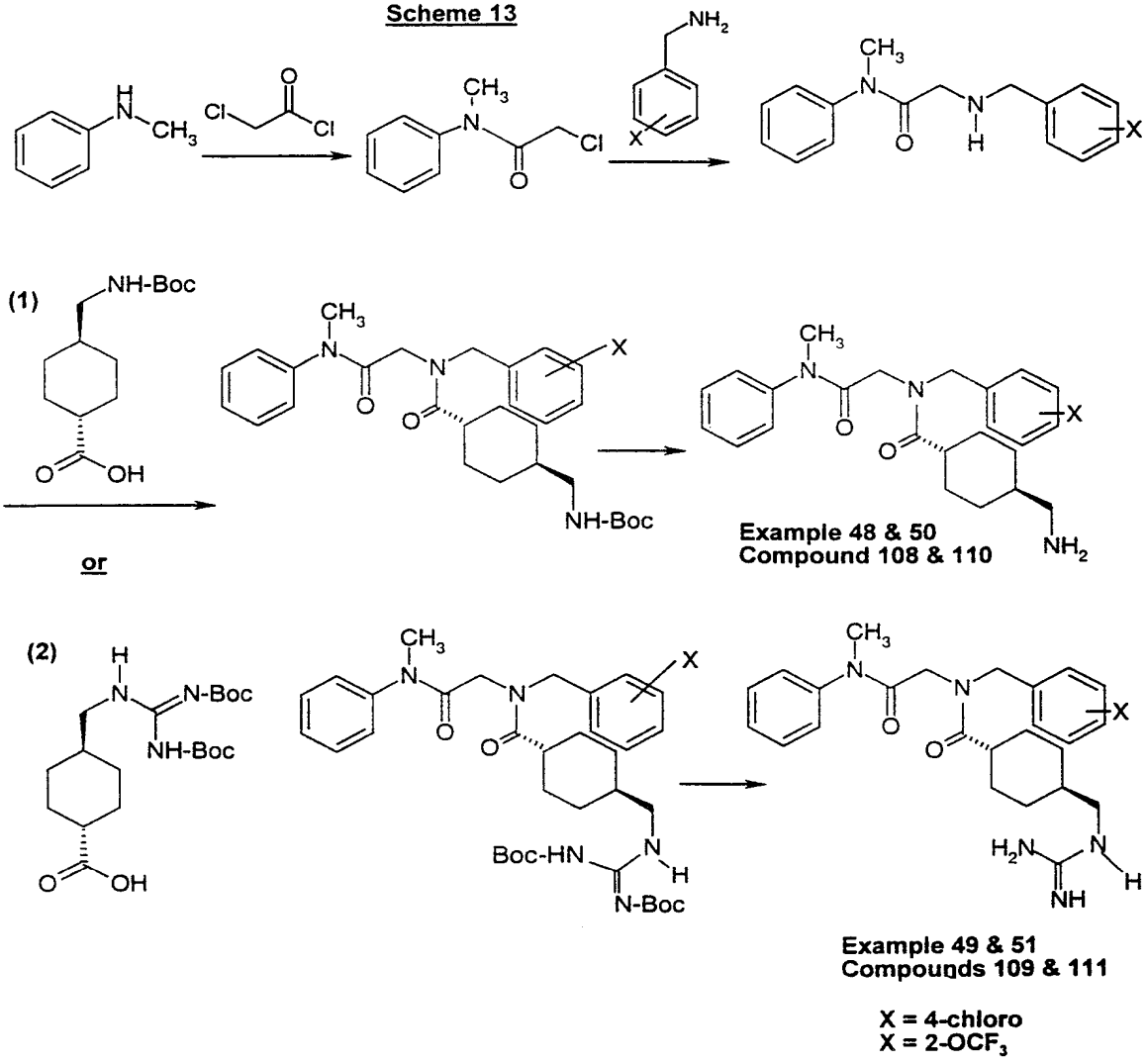
^{1}H NMR (MeOD-d_4) d 7.40 (m, 4H), 7.05 (m,2H), 6.8 (d, 2H), 6.6 (m, 2H), 3.5 (m, 2H), 3.0 (m, 4H), 2.75 (t, 2H), 1.9 - 0.75 (broad m, 10H).

MS(APCI): 409.27

Examples 48-51

The **compounds 108-111** of Examples 48-51 were prepared by following the synthetic route described in **Scheme 13** below.

Scheme 13


(1)
NH-Boc
OH
or
(2)
N-Boc
NH-Boc
OH
Boc-HN
N-Boc
NH-Boc
Example 48 & 50
Compound 108 & 110
Example 49 & 51
Compounds 109 & 111
X = 4-chloro
X = 2-OCF3

These compounds were synthesized by alkylating the appropriate primary amines by N-methyl chloroacetanilide to give the secondary amines. The secondary amines were then condensed with either *trans*-4-N-(diBoc)-guanidinomethyl cyclohexane-1-carboxylic acid or *trans*4-N-(Boc)-aminomethyl cyclohexane-1-carboxylic acid to form a new amide bond via BOP reagent as described in General Procedure for amide bond formation. Finally the amine protecting group (Boc) was removed by acid treatment as described in General Procedure to provide the desired products.

Step 1

Preparation of *trans*-Methyl 4-aminomethyl cyclohexane-1-carboxylate

To a cooled suspension of *trans*-4-aminomethyl cyclohexane-1-carboxylic acid (25 g, 0.159 mol) in dry methanol (200 mL) was added thionyl chloride (17.4 mL, 0.238 mol) dropwise. After standing overnight, the solvent and excess reagent were evaporated. The hydrochloride salt was partitioned between diethyl ether and saturated potassium carbonate. The ether layer was dried over magnesium sulfate and evaporated to a colorless oil.

Step 2

Preparation of Methyl *trans*-4-N-(diBoc)-guanidinomethyl cyclohexane-1-carboxylate

trans-Methyl 4-aminomethyl cyclohexane-1-carboxylic acid (8.61 g, 50.29 mmol) was dissolved in THF (80 mL) and a solution of 1-H-pyrazole-1-(N,N-*bis*(tert-butoxycarbonyl)carboxamidine (15.59 g, 50.29 mmol) in THF was added. After stirring at r.t. for 3 h, solvent was evaporated. The residue was redissolved in diethyl ether, washed with water, dil. HCl solution, saturated sodium bicarbonate, brine, dried over magnesium sulfate and evaporated to a solid, 19.6 g (94%).

Step 3

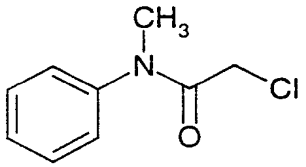
Preparation of *trans*-4-N-(diBoc)-guanidinomethyl cyclohexane-1-carboxylic acid

To a solution of methyl *trans*-4-N-(diBoc)-guanidinomethyl cyclohexane-1-carboxylic acid (19.5 g, 47.2 mmol) in dry THF (200 mL) was added potassium trimethylsilanolate (12.1 g, 94.4 mmol). The mixture was stirred at r.t. overnight. It was diluted with ethyl acetate/water. The organic layer was dried over magnesium sulfate and evaporated to give a solid residue.

Step 4

Preparation of N-methyl chloroacetanilide

To a solution of N-methylaniline (1.5 eq) in dichloromethane at 0 °C was added a solution of chloroacetylchloride (1 eq) in dichloromethane dropwise. The reaction was stirred at room temperature for 20 minutes before it was diluted with dichloromethane and washed with 1 N HCl (2x), saturated aqueous $NaHCO_3$ (2x), brine, and dried over $MgSO_4$. Upon filtration and evaporation of the solvent, the product was obtained as a yellow solid.

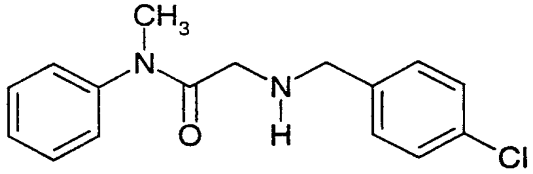


MS (APCI) : 183.95.

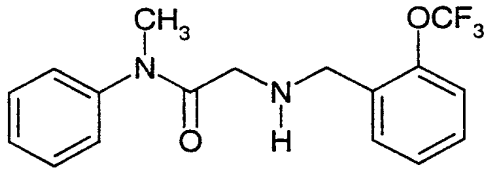
Step 5

Amination of N-methyl chloroacetanilide

A solution of the N-methyl chloroacetanilide (1 eq), triethylamine (2 eq), and a primary amine (1 eq) in dichloromethane was stirred at room temperature overnight. The reaction was diluted with dichloromethane and extracted with an aqueous solution of $NaHCO_3$, brine, and dried over MgSO4. The sample was concentrated and purified by silica gel flash column chromatography using ethyl acetate/hexane. Specific examples are provided below:



^{1}H-NMR ($CDCl_3$): 7.4 (m, 2H), 7.2 (m, 3H), 7.1 (m, 2H), 3.6 (s, 2H), 3.4 (s, 3H), and 3.1 (s, 2H).



The **compounds 108, 109, 110 and 111** of Examples 48-51 were prepared as described above. The results are presented in Table 4 below.

Table 4

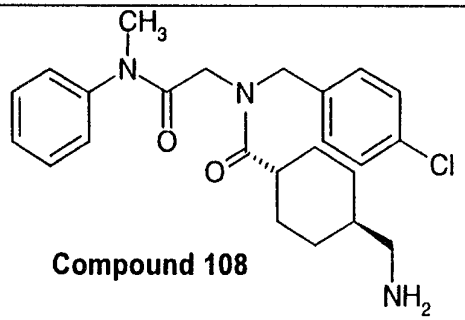
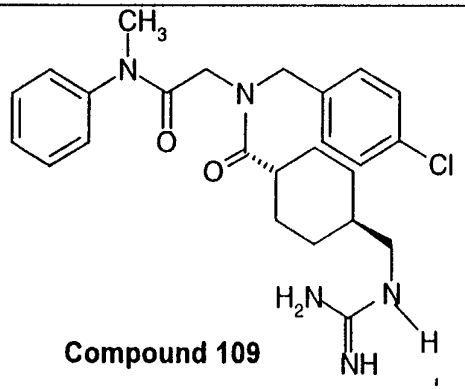
Ex	Structure	Chemical name	Physical Characterization
48	 **Compound 108**	*trans*-4-aminomethyl-N-(4-chlorobenzyl-N,N-methylphenyl-2-acetyl) cyclohexane carboxamide	**MS (FAB):** 428
49	 **Compound 109**	*trans*-4-(guanidinomethyl)-N-(4-chlorobenzyl-N,N-methylphenyl-2-acetyl)-cyclohexane carboxamide	**^{1}H NMR (MeOD-d_4)** δ 7.5 (m, 4H), 7.4 (m, 2H), 7.2 (m, 3H), 4.7 (2s, 1H), 4.5 (2s, 1H), 4.1 (2s, 1H), 3.7 (s, 1H), 3.3 (d, 2H), 3.2 (s, 3H), 1.8 (m, 4H), 1.45 (m, 3H), and 1.5 (m, 2H). **MS (FAB):** 470

Table 4 (contd.)

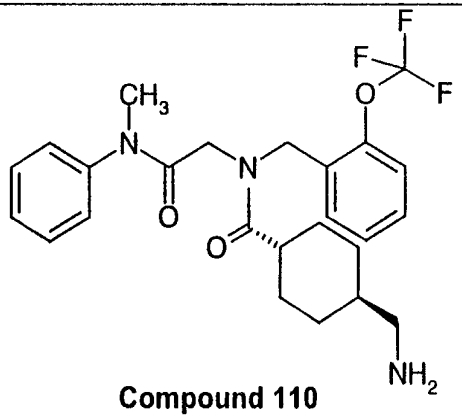
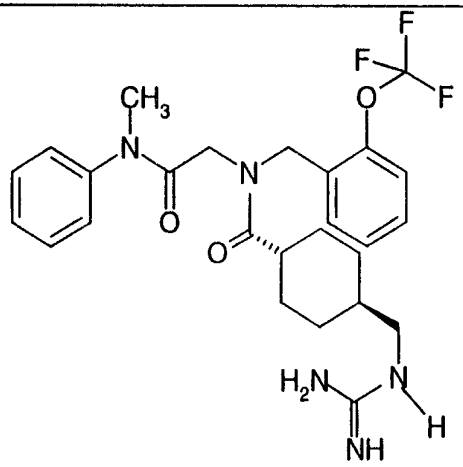
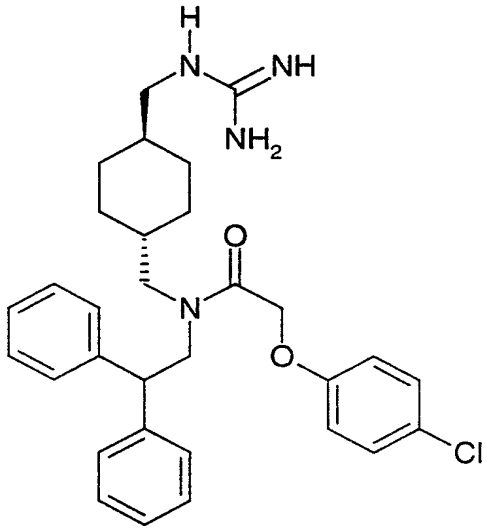
Ex	Structure	Chemical name	Physical Characterization
50	 Compound 110	*trans*-4-(aminomethyl)-N-(2-trifluoromethoxybenzyl-N,N-methylphenyl-2-acetyl) cyclohexane carboxamide	**^{1}H NMR (MeOD-d_4)** δ 7.6 (m, 2H), 7.4 (m, 3H), 7.3 (m, 2H), 7.2 (m, 2H), 4.8 (d, 1H), 2.8 dd, 2H), 2.6 (m, 1H), 1.8 (m, 4H), 1.5 (m, 3H), and 1.2 (m, 2H). **MS (FAB):** 478.

Table 4 (contd.)

Ex	Structure	Chemical name	Physical Characterization
51	 Compound 111	*trans*-4-(guanidinomethyl)-N-(2- trifluoromethoxybenzyl-N,N-methylphenyl-2-acetyl)cyclohexane carboxamide	**^{1}H NMR (MeOD- d_4) δ** 7.5 (m, 2H), 7.4 (m, 3H), 7.3 (m, 2H), 7.2 (m, 2H), 4.1 (qt, 2H), 3.8 (d, 2H), 3.2 (d, 3H), 2.9 (s, 2H), 2.8 (m, 1H), 2.4 (m, 1H), 1.7 (m, 3H), 1.3 (m, 2H), and 0,8 (m, 2H). **MS (FAB):** 520

Example 52
Preparation of *trans*-1-[N-(2,2-diphenylethyl)-N-(p-chlorophenoxyacetyl)] aminomethyl-4-guanidinomethyl cyclohexane hydrochloride (compound 112)



(112)

The acylation was carried out according to the General procedure for acylation of secondary amines: *trans*-4-N-(diBoc)guanidinomethyl-1-N-(2,2-diphenylethyl)aminomethyl cyclohexane (0.20 g, 0.35 mmol) was reacted with 4-chlorophenoxyacetyl chloride (61.5 mg, 0.3 mmol). The acylated product was purified by silica gel chromatography using a mixture of hexane-ethyl acetate as the eluent.

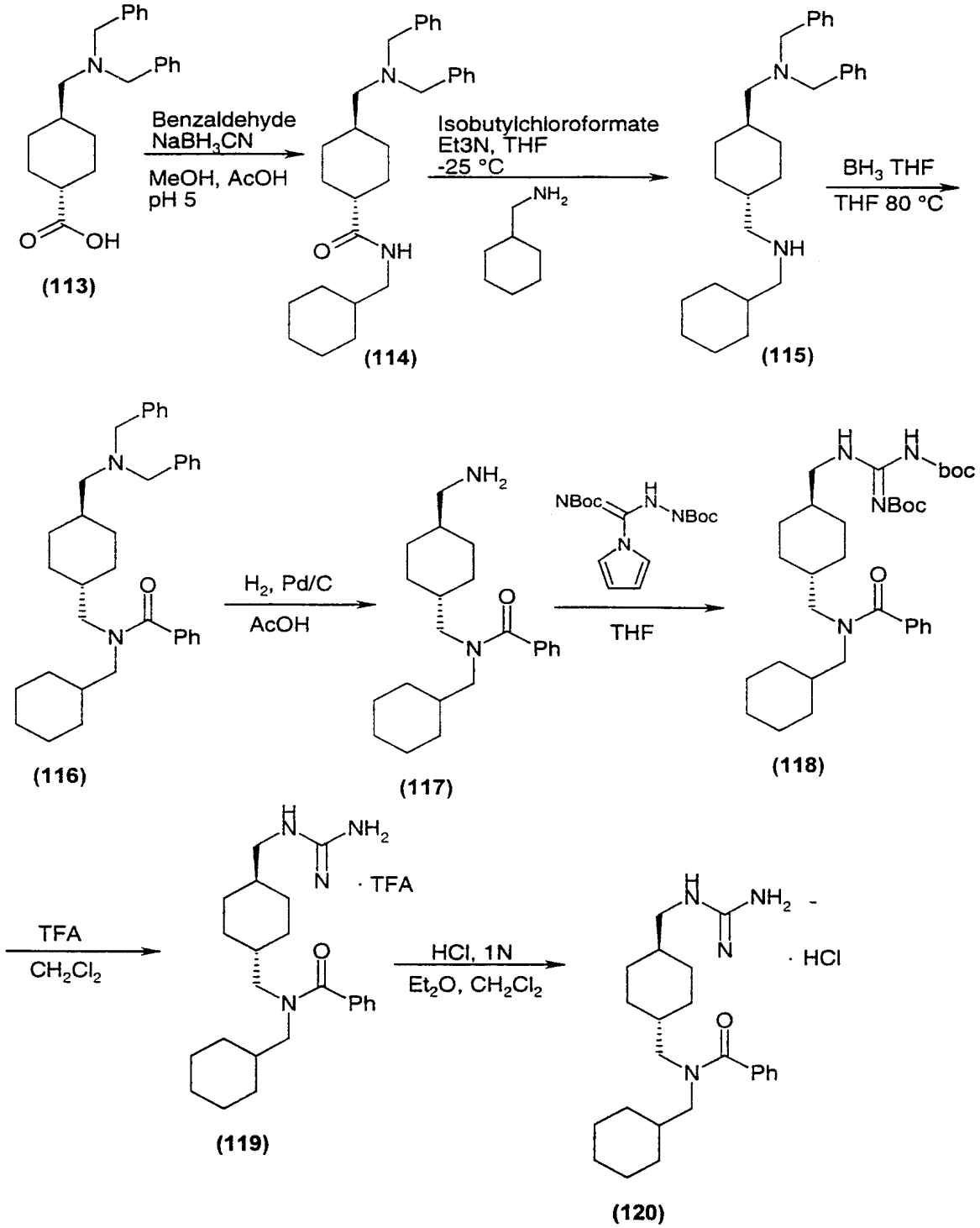
MS: 733.4 (M+H) .

The above compound was deprotected according to General procedure for deprotection of diBoc-guanidino compounds to give the free guanidino-**compound 112** as the hydrochloride salt

MS: 533.4 (M+H).

Example 53
Preparation of *trans*-1-N-(cyclohexylmethyl)-N-(benzoyl)-aminomethyl-4-guanidinomethyl cyclohexane hydrochloride (compound 120)

Scheme 14


Ph
N
Ph
O
OH
(113)
Benzaldehyde
NaBH3CN
MeOH, AcOH
pH 5
NH
(114)
Isobutylchloroformate
Et3N, THF
-25 °C
NH2
(115)
BH3 THF
THF 80 °C
(116)
H2, Pd/C
AcOH
(117)
NBoc
NBoc
THF
boc
(118)
TFA
CH2Cl2
TFA
(119)
HCl, 1N
Et2O, CH2Cl2
HCl
(120)

(i) Preparation of *trans*-4 N,N-(Dibenzyl)-aminomethyl cyclohexane carboxylic acid (compound 113)

To a suspension of (40.0 g, 254.4 mmol) of trans-4-(aminomethyl)cyclohexanecarboxylic acid, in 1.5 L of methanol was added benzaldehyde (60 ml, 590.8 mmol) followed by sodium cyanoborohydride (16g, 254.6 mmol). The pH was then adjusted to approx. 5 with glacial acetic acid. The reaction was allowed to stir for 48 hrs, during which the pH is monitored and adjusted to 5 as needed, after which the reaction volume was then decreased and the pH adjusted to 9 with 1 N NaOH. The reaction was then extracted repeatedly with diethyl ether. The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated. Product solidifies on standing and was recrystallized from methanol giving 32 g of impure product which was used without further purification in the next step

The monobenzyl was isolated as a white solid, which formed during the extraction and was collected by filtration. (8.2g)

Monobenzyl ^{1}H NMR: (400 MHz, D_2O) δ: (2H, m, 0.81-0.91), (2H, m, 1.11-1.22), (1H, m, 1.51-1.56), (2H, m, 1.62, 1.64) (2H, m, 1.72-1.75), (1H, m, 1.87-1.95), (NCH_2, 2H, d, J = 7.2), (CH_2Ar, 5H, s)

^{13}C NMR: (100, D_2O, DSS) δ 31.43 (CH_2), 31.88 (CH_2), 36.81(CH), 48.95 (CH), 54.01 (NCH_2), 55.35 (NCH_2), 131.94 (CH), 132.37 (CH), 132.60 (CH), 133.30 (C), 188.43 (C=O)

(ii) Preparation of *trans*-1-N-(Cyclohexylmethyl)-4-N,N-(dibenzyl)-aminomethylcyclohexane carboxamide (compound 114)

To a solution of the acid **(compound 113)** (8.11 g, 24.07 mmol, 1 eq) in THF (150 mL) at –25 °C was added Et_3N (4.02 ml, 28.88 mmol, ml 1.2 eq) followed by chloroformate (3.75 ml, 28.88 mmol, 1.2 eq) Aloud to react for 30 mins then added cyclohexanemethylamine (4.7 ml, 36.11 mmol, 1.5 eq). Strirred over night, added saturated NH_4Cl, extracted 3 X

with ethyl acetate, dried over $MgSO_4$. Purified by MPLC, 5 % $MeOH/CH_2Cl_2$. Yielded 10.4 g, 100%

(iii) Preparation of *trans*-1-N-(Cyclohexylmethyl)-aminomethyl-4-N,N-(dibenzyl) aminomethyl cyclohexane (compound 115)

To a solution of amide **(compound 114)** in THF 100 mL was added BH_3·THF 1M (71.9 mL, 71.9 mmol, 3 eq). The reaction was heated at reflux for 12 hrs. 80 °C. Then cooled down to RT. A solution of 1 N HCl was added slowly and the mixture was heated at reflux for 3 hrs. The mixture was extracted 4 times with CH2Cl2. washed with $NaHCO_3$ then dried over $MgSO_4$. Purified by MPLC. Yielded 7.37 g, 74 %.

(iv) Preparation of *trans*-*N*-[[4-[[bis(phenylmethyl)amino]methyl] cyclohexyl]methyl]-*N*-(cyclohexylmethyl)-benzamide. (compound 116)

To a solution of **(compound 115)** (740 mg, 1.77 mmol, 1 eq) in CH_2Cl_2 (10ml) was added Et_3N (0.492 ml, 3.54 mmol, 2 eq) followed by benzoyl chloride (0.322 ml, 2.66 mmol, 1.5 eq). The reaction was allowed to stir over night. Saturated NH_4Cl was added and the reaction was extracted 3 times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The product was purified by silica gel flash chromatography using hexanes:ethyl acetate; 4:1. Yielded 675 mg, 73 %

(v) Preparation of trans, *N*-[[4-(aminomethyl)cyclohexyl]methyl]-*N*-(cyclohexylmethyl)-benzamide (Compound 117)

To a solution of **(compound 116)** (675 mg, 1.29 mmol) in acetic acid (100 ml) was added Pd/C 10 % 70 mg. This was placed on a Parr apparatus under H_2 at 50 PSI and 70 °C overnight. Reaction was filtered through celite and concentrated. The extract was washed with $NaHCO_3$ then extracted 3 times with CH_2Cl_2. Purification was done by silica gel flash chromatography. CH_2Cl_2:MeOH:8:2. Yielded 386 mg of a clear oil, 88 %.

(vi) Preparation of *trans*-1-N-(cyclohexylmethyl)-N-(benzoyl)-aminomethyl-4-(di-t-butyl carbonyloxy)-guanidinomethyl cyclohexane (compound 118)

To a solution of **(compound 117)** (140 mg, 0.55 mmol, 1 eq) in THF 3 mL at RT was added 133 mg, 0.61 mmol, 1.1 eq) The reaction was stirred for 48 hrs then concentrated un reduced pressure. Purified by flash chromatography on silica gel with 8:2 hex/Ethyl Acetate. Yielded 251 mg, 77 yield.

(vii) Preparation of *trans*-1-N-(cyclohexylmethyl)-N-(benzoyl)-aminomethyl-4-guanidinomethyl cyclohexane trifluoroacetate (compound 119)

To a solution of **(compound 117)** (250 mg) in CH_2Cl_2 (5 mL) at RT wad added dropwise TFA. The mixture was allowed to stir 3 hrs then the reaction was concentrated. The product was washed with NaOH then extracted 3 times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered then concentrated. Yielded 163 mg, 100%

(viii) Preparation of *trans*-1-N-(cyclohexylmethyl)-N-(benzoyl)-aminomethyl-4-guanidinomethyl cyclohexane hydrochloride (compound 120)

To a solution of **(compound 118)** (163mg) in CH_2Cl_2/Et_2O (2ml/2ml) was added 1 N HCl in Et_2O (1 mL). The mixture was allowed to stir at RT for 2 Hrs. It was then concentrated and purified by MPLC 20 % to 50 % CH_3CN/H_2O. Yielded 117 mg of a white powder, 66 %.

(400 MHz, CDCl3, TMS, Free amine, equilibrium):7.37 (s, 3H, C=CH), 7.31 (s, 2H, C=CH), 3.40 (s broad, 2H, CH2N), 3.10 (d, 2H, CH2N), 2.90 and, 2.82 (d and d, 2H, CH2N), 1.81-1.48 (m, 13H, CH2, NH), 1.26-0.80 (m, 10H, CH, CH2), 0.61-0.58 (m, 2H. CH2).

C23H36N4O X 1.3 HCl, X 0.1 H2O, X 0.4 C4H10O Found: C 63.75% H 8.84%, N 11.95% Calc.:C 63.76%, H 9.03%, N 12.09%, O5.18%, Cl 9.95%.

Pharmaceutical compositions

The novel compounds according to the present invention may be administered orally, intramuscularly, subcutaneously, topically, intranasally, intraperitoneally, intrathoracially, intravenously, epidurally, intrathecally, intracerebroventricularly and by injection into the joints.

A preferred route of administration is orally, intravenously or intramuscularly.

The dosage will depend on the route of administration, the severity of the disease, age and weight of the patient and other factors normally considered by the attending physician, when determining the individual regimen and dosage level as the most appropriate for a particular patient.

For preparing pharmaceutical compositions from the compounds of this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories.

A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or tablet disintegrating agents; it can also be an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

For preparing suppository compositions, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture is then poured into convenient sized molds and allowed to cool and solidify.

Suitable carriers are magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

Pharmaceutically acceptable salts are acetate, benzenesulfonate, benzoate, bicarbonate, bitartrate, bromide, calcium acetate, camsylate, carbonate, chloride, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, glucaptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, pamoate (embonate), pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, teoclate, triethiodide, benzathine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine, procaine, aluminium, calcium, lithium, magnesium, potassium, sodium, and zinc.

Preferred pharmaceutically acceptable salts are the hydrochlorides, trifluoroacetates and bitartrates.

The term composition is intended to include the formulation of the active component with encapsulating material as a carrier providing a capsule in which the active component (with or without other carriers) is surrounded by a carrier which is thus in association with it. Similarly, cachets are included.

Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

Liquid from compositions include solutions, suspensions, and emulsions. Sterile water or water-propylene glycol solutions of the active compounds may be mentioned as an

example of liquid preparations suitable for parenteral administration. Liquid compositions can also be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions for oral administration can be prepared by dissolving the active component in water and adding suitable colorants, flavoring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

Preferably the pharmaceutical compositions is in unit dosage form. In such form, the composition is divided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of the preparations, for example, packeted tablets, capsules, and powders in vials or ampoules. The unit dosage form can also be a capsule, cachet, or tablet itself, or it can be the appropriate number of any of these packaged forms.

BIOLOGICAL EVALUATION

A) IN VITRO MODEL

Cell culture

Human 293S cells expressing cloned human μ, δ, and κ receptors and neomycin resistance were grown in suspension at 37°C and 5% CO_2 in shaker flasks containing calcium-free DMEM10% FBS, 5% BCS, 0.1% Pluronic F-68, and 600 μg/ml geneticin.

Membrane preparation

Cells were pelleted and resuspended in lysis buffer (50 mM Tris, pH 7.0, 2.5 mM EDTA, with PMSF added just prior to use to 0.1 mM from a 0.1 M stock in ethanol), incubated on ice for 15 min, then homogenized with a polytron for 30 sec. The suspension was spun at 1000g (max) for 10 min at 4°C. The supernatant was saved on ice and the pellets resuspended and spun as before. The supernatants from both spins were combined and spun at 46,000 g(max) for 30 min. The pellets were resuspended in cold Tris buffer (50 mM Tris/Cl, pH 7.0) and spun again. The final pellets were resuspended in membrane buffer (50 mM Tris, 0.32 M sucrose, pH 7.0). Aliquots (1 ml) in polypropylene tubes were frozen in dry ice/ethanol and stored at -70°C until use. The protein concentrations were determined by a modified Lowry assay with SDS.

Binding assays

Membranes were thawed at 37°C, cooled on ice, passed 3 times through a 25-gauge needle, and diluted into binding buffer (50 mM Tris, 3 mM $MgCl_2$, 1 mg/ml BSA (Sigma A-7888), pH 7.4, which was stored at 4°C after filtration through a 0.22 m filter, and to which had been freshly added 5 µg/ml aprotinin, 10 µM bestatin, 10 µM diprotin A, no DTT). Aliquots of 100 µl (for µg protein, see Table 1) were added to iced 12x75 mm polypropylene tubes containing 100 µl of the appropriate radioligand (see Table 1) and 100 µl of test peptides at various concentrations. Total (TB) and nonspecific (NS) binding were determined in the absence and presence of 10 µM naloxone respectively. The tubes were vortexed and incubated at 25°C for 60-75 min, after which time the contents are rapidly vacuum-filtered and washed with about 12 ml/tube iced wash buffer (50 mM Tris, pH 7.0, 3 mM $MgCl_2$) through GF/B filters (Whatman) presoaked for at least 2h in 0.1% polyethyleneimine. The radioactivity (dpm) retained on the filters was measured with a beta counter after soaking the filters for at least 12h in minivials containing 6-7 ml scintillation fluid. If the assay is set up in 96-place deep well plates, the filtration is over 96-place PEI-soaked unifilters, which were washed with 3 x 1 ml wash buffer, and dried in

an oven at 55°C for 2h. The filter plates were counted in a TopCount (Packard) after adding 50 µl MS-20 scintillation fluid/well.

Data analysis

The specific binding (SB) was calculated as TB-NS, and the SB in the presence of various test peptides was expressed as percentage of control SB. Values of IC_{50} and Hill coefficient (n_H) for ligands in displacing specifically bound radioligand were calculated from logit plots or curve fitting programs such as Ligand, GraphPad Prism, SigmaPlot, or ReceptorFit. Values of K_i were calculated from the Cheng-Prussoff equation. Mean ± S.E.M. values of IC_{50}, K_i and n_H were reported for ligands tested in at least three displacement curves.

Receptor saturation experiments

Radioligand K_δ values were determined by performing the binding assays on cell membranes with the appropriate radioligands at concentrations ranging from 0.2 to 5 times the estimated K_δ (up to 10 times if amounts of radioligand required are feasable). The specific radioligand binding was expressed as pmole/mg membrane protein. Values of K_δ and B_{max} from individual experiments were obtained from nonlinear fits of specifically bound (B) vs. nM free (F) radioligand from individual according to a one-site model.

B) BIOLOGICAL MODEL (IN VIVO MODEL)

FREUND'S COMPLETE ADJUVANT (FCA), AND SCIATIC NERVE CUFF INDUCED MECHANO-ALLODYNIA IN RAT

Animals

Male Sprague-Dawley rats (Charles River, St-Constant, Canada) weighing 175-200g at the time of surgery were used. They were housed in groups of three in rooms thermostatically maintained at 20° C with a 12:12 hr light/dark cycle, and with free access to food and water. After arrival, the animals were allowed to acclimatize for at least 2 days before surgery. The experiments were approved by the appropriate Medical Ethical Committee for animal studies.

EXPERIMENTAL PROCEDURE

FREUND'S COMPLETE ADJUVANT

The rats were first anesthetized in a Halothane chamber after which 10µl of FCA was injected s.c. into the dorsal region of the left foot, between the second and third external digits. The animals were then allowed to recover from anesthesia under observation in their home cage.

SCIATIC NERVE CUFF

The animals were prepared according to the method described by Mosconi and Kruger (1996). Rats were anesthetized with a mixture of Ketamine / Xylazine i.p. (2ml/kg) and placed on their right side and an incision made over, and along the axis of, the lateral aspect of the left femur. The muscles of the upper quadriceps were teased apart to reveal the sciatic nerve on which a plastic cuff (PE-60 tubing, 2mm long) was placed around. The wound was then closed in two layers with 3-0 vicryl and silk sutures.

DETERMINATION OF MECHANO-ALLODYNIA USING VON FREY TESTING

Testing was performed between 08:00 and 16:00h using the method described by Chaplan et al. (1994). Rats were placed in Plexiglas cages on top of a wire mesh bottom which allowed access to the paw, and were left to habituate for 10-15 min. The area tested was

the mid-plantar left hind paw, avoiding the less sensitive foot pads. The paw was touched with a series of 8 Von Frey hairs with logarithmically incremental stiffness (0.41, 0.69, 1.20, 2.04, 3.63, 5.50, 8.51, and 15.14 grams; Stoelting, Ill, USA). The von Frey hair was applied from underneath the mesh floor perpendicular to the plantar surface with sufficient force to cause a slight buckling against the paw, and held for approximately 6-8 seconds. A positive response was noted if the paw was sharply withdrawn. Flinching immediately upon removal of the hair was also considered a positive response. Ambulation was considered an ambiguous response, and in such cases the stimulus was repeated.

TESTING PROTOCOL

The animals were tested on postoperative day 1 for the FCA-treated group and on post-operative day 7 for the Sciatic Nerve Cuff group. The 50% withdrawal threshold was determined using the up-down method of Dixon (1980). Testing was started with the 2.04 g hair, in the middle of the series. Stimuli were always presented in a consecutive way, whether ascending or descending. In the absence of a paw withdrawal response to the initially selected hair, a stronger stimulus was presented; in the event of paw withdrawal, the next weaker stimulus was chosen. Optimal threshold calculation by this method requires 6 responses in the immediate vicinity of the 50% threshold, and counting of these 6 responses began when the first change in response occurred, e.g. the threshold was first crossed. In cases where thresholds fell outside the range of stimuli, values of 15.14 (normal sensitivity) or 0.41 (maximally allodynic) were respectively assigned. The resulting pattern of positive and negative responses was tabulated using the convention, X = no withdrawal; O = withdrawal, and the 50% withdrawal threshold was interpolated using the formula:

$$50\%\ \text{g threshold} = 10^{(Xf + k\delta)} / 10{,}000$$

where Xf = value of the last von Frey hair used (log units); k = tabular value (from Chaplan et al. (1994)) for the pattern of positive / negative responses; and δ = mean difference between stimuli (log units). Here $\delta = 0.224$.

Von Frey thresholds were converted to percent of maximum possible effect (% MPE), according to Chaplan et al. 1994. The following equation was used to compute % MPE:

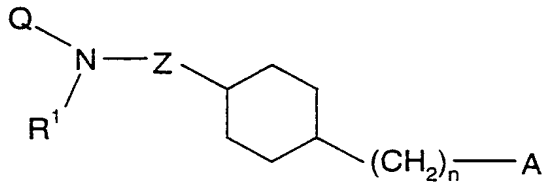
$$\% \text{ MPE} = \frac{\text{Drug treated threshold (g) - allodynia threshold (g)}}{\text{Control threshold (g) - allodynia threshold (g)}} \times 100$$

ADMINISTRATION OF TEST SUBSTANCE

Rats were injected (subcutaneously, intraperitoneally, or orally) with a test substance prior to von Frey testing, the time between administration of test compound and the von Frey test varied depending upon the nature of the test compound.

CLAIMS

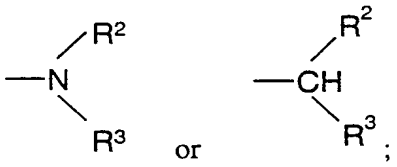
1. A compound according to formula I



I

wherein

A is



wherein R^2 and R^3 are as defined below;

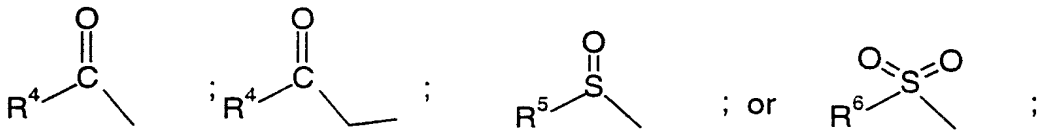
Z is $(CH_2)_m$ or a carbonyl group;

m and n are each and independently an integer of from 0-3, and one or more of the hydrogens in such an alkylene-chain may optionally be substituted by anyone of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, or hydroxy; *or*

one or more of the methylene groups may optionally be substituted by a heteroatom such as O, N or S;

m and n may not both be 0;

Q is selected from any of CH_3;



wherein

R^4, R^5 and R^6 is each and independently selected from any of

(i) C_6-C_{10} aryl; or

(ii) heteroaryl having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; and

wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined below;

(iii) hydrogen;

(iv) a straight or branched C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl;

(v) C_1-C_3 alkoxy;

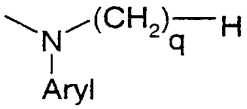
(vi) saturated or unsaturated C_3 - C_{10} cycloalkyl, optionally and independently substituted by one or more aryl groups or heteroaryl groups having from 5 to 10 atoms with the heteroatom(s) being selected from any of S, N and O and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined below;

(vii) -[$(CH_2)_q$-aryl] where q is an integer of from 1-3, and the aryl may optionally be substituted by 1 or 2 substituents Y, where each Y is as defined below;

(viii) -[$(CH_2)_r$-heteroaryl] where r is an integer of from 1-3, the heteroaryl having from 5 to 10 atoms with heteroatoms(s) being selected from any of S, N, and O, optionally and independently substituted by 1 or 2 substituents Y as defined below;

(ix) -[CH_2-O-aryl] where the aryl may optionally be substituted by 1 or 2 substituents Y, where each Y is as defined below;

(x)



where q is an integer of from 1-3, and the aryl is as defined below, optionally substituted by 1 or 2 substituents Y, where each Y is as defined below;

R^1 is selected from anyone of

(i) a straight or branched C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, where each alkyl, alkenyl or alkynyl may optionally be substituted by one or more aromatic or heteroaromatic substituents;

(ii) C_3-C_7 cycloalkyl, optionally comprising one or more unsaturations and optionally substituted by one or more of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, hydroxy; or substituted by one or more aryl(s), or heteroaryl(s) having from 5 to 10 atoms and the heteroatom(s) being selected from any of S, N and O and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined below;

(iii) hydrogen, halogen or C_1-C_6 alkoxy;

(iv) C_6-C_{10} aryl;

(v) heteroaryl having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined below;

(vi) 9,10-dihydro-9,10-ethanoantracenyl;

(vii) -[$(CH_2)_q$-aryl] where q is an integer of from 1-3 and the aryl may optionally be substituted by 1 or 2 substituents Y, where each Y is as defined below;

(viii) -[$(CH_2)_r$-heteroaryl] where r is an integer of from 1-3, the heteroaryl having from 5 to 10 atoms and the heteroatoms(s) being selected from any of S, N, and O, and wherein the heteroatom(s) may optionally and independently be substituted by 1 or 2 substituents Y, where each Y is as defined below;

(ix) -[$(CH_2)_q$-aryl-O-$(CH_2)_r$-aryl] where q and r is each and independently an integer of from 1-3;

(x) -$(CH_2)_q$-[C_3-C_6 cycloalkyl] where q is from 1-2, optionally substituted by 1 or 2 substituents Y and wherein Y is as defined below;

R^2 is selected from any of

(i) hydrogen;

(ii) a straight or branched C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, where each alkyl, alkenyl or alkynyl may optionally be substituted by one or more aromatic or heteroaromatic substituents;

(iii) C_6 - C_{10} arylalkyl, wherein the aryl may optionally be substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined below;

(iv) heteoaryl-(C_5 - C_{10} alkyl), where the heteroaryl has from 5 to 10 atoms and the heteroatom being selected from any of S, N and O, and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined below;

(v) C_3-C_{10} cycloalkyl, optionally comprising one or more unsaturations and optionally susbtituted by one or more heteroaryl(s) where the heteroaryl has from 5 to 10 atoms and the heteroatom being selected from any of S, N and O;
and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined below;

(vi) C_6-C_{10} aryl, optionally and independently substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom(s) being selected from any of S, N and O and wherein the heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined below;

(vii) heteroaryl having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined below;

R^3 is selected from anyone of

(i) hydrogen;

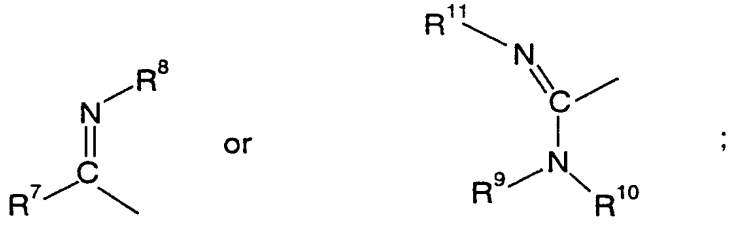
(ii) a straight or branched C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, where each alkyl, alkenyl or alkynyl may optionally be substituted by one or more aromatic or heteroaromatic substituents;

(iii) C_6 - C_{10} arylalkyl, wherein the aryl may optionally be substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined below;

(iv) heteoaryl-(C_5 - C_{10} alkyl), where the heteroaryl has from 5 to 10 atoms and the heteroatom being selected from any of S, N and O, and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined below;

(v) C_3-C_{10} cycloalkyl, optionally comprising one or more unsaturations and optionally substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O, and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined below;

(vi)



;

wherein

R^7, R^8, R^9, R^{10} and R^{11} is each and independently selected from

(a) hydrogen;

(b) a straight or branched C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, where each alkyl, alkenyl or alkynyl may optionally be substituted by one or more aromatic or heteroaromatic substituents;

(c) C_6 - C_{10} arylalkyl, wherein the aryl may optionally be substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined below;

(d) heteoaryl-(C_5 - C_{10} alkyl), where the heteroaryl has from 5 to 10 atoms and the heteroatom being selected from any of S, N and O, and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined below;

(e) C_3-C_{10} cycloalkyl, optionally comprising one or more unsaturations and optionally susbtituted by one or more heteroaryl(s) where the heteroaryl has from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined below;

(f) C_6-C_{10} aryl, optionally and independently substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom(s) being selected from any of S, N and O and wherein the heteroaryl may optionally and

independently be substituted by 1 or 2 substituents Y wherein each Y is as defined below;

or

R^2 and R^3 may optionally form a heterocyclic ring;

Y is each and independently selected from any of hydrogen, CH_3; —$(CH_2)_{p1}CF_3$; halogen; C_1-C_3 alkoxy; hydroxy; -NO_2; -OCF_3; —$CONR^aR^b$; —$COOR^a$; —COR^a; —$(CH_2)_{p2}NR^aR^b$; —$(CH_2)_{p3}CH_3$, $(CH_2)_{p4}SOR^aR^b$; —$(CH_2)_{p5}SO_2R^a$; —$(CH_2)_{p6}SO_2NR^a$; C_4-C_8(alkyl-cycloalkyl) wherein alkyl is C_1-C_2 alkyl and cycloalkyl is C_3-C_6 cycloalkyl; and 1 or 2 heteroaryl(s) having from 5 to 10 atoms and the heteroatom(s) being selected from any of S, N and O; and oxides such as N-oxides or sulfoxides; and wherein

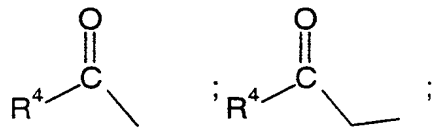
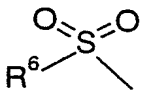
R^a and R^b is each and independently selected from hydrogen, a branched or straight C_1-C_6 alkyl, C_1-C_6 alkenyl, C_3-C_8 cycloalkyl; and wherein
p1, p2, p3, p4, p5 and p6 is each and independently 0, 1 or 2;

as well as pharmaceutically acceptable salts, isomers, hydrates, isoforms and prodrugs thereof.

2. A compound according to formula I of claim 1, wherein

m and n are each and independently an integer of from 1-3;

Q is selected from any of CH_3;


;
; and 
;

wherein

R^4 and R^6 is each and independently selected from any of

(i) C_6-C_{10} aryl; or

(ii) heteroaryl having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; and

wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined in claim 1;

(iii) a straight or branched C_1-C_6 alkyl or C_2-C_6 alkenyl;

(iv) C_1-C_3 alkoxy;

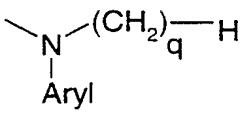
(v) saturated or unsaturated C_3 - C_6 cycloalkyl, optionally and independently substituted by one or more aryl groups or heteroaryl groups having from 5 to 10 atoms with the heteroatom(s) being selected from any of S, N and O and wherein the aryl, heteroaryl and cycloalkyl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined in claim 1;

(vi) -[$(CH_2)_q$-aryl] where q is an integer of from 1-3, and the aryl may optionally be substituted by 1 or 2 substituents Y, where each Y is as defined in claim 1;

(vii) -[$(CH_2)_r$-heteroaryl] where r is an integer of from 1-3, the heteroaryl having from 5 to 10 atoms with heteroatoms(s) being selected from any of S, N, and O, optionally and independently substituted by 1 or 2 substituents Y as defined in claim 1;

(viii) -[CH_2-O-aryl] where the aryl may optionally be substituted by 1 or 2 substituents Y, where each Y is as defined in claim 1;

(ix)



where q is an integer of from 1-2, and the aryl is as defined below, optionally substituted by 1 or 2 substituents Y, where each Y is as defined in claim 1;

R^1 is selected from anyone of

(i) a straight or branched C_1-C_6 alkyl or C_2-C_6 alkenyl, where each alkyl and alkenyl may optionally be substituted by one or more aromatic or heteroaromatic substituents;

(ii) C_3-C_7 cycloalkyl, optionally comprising one or more unsaturations and optionally substituted by one or more of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, hydroxy; or substituted by one or more aryl(s), or heteroaryl(s) having from 5 to 10 atoms and the heteroatom(s) being selected from any of S, N and O and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined in claim 1;

(iii) hydrogen, halogen or C_1-C_6 alkoxy;

(iv) C_6-C_{10} aryl;

(v) heteroaryl having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined in claim 1;

(vi) 9,10-dihydro-9,10-ethanoantracenyl;

(vii) -[$(CH_2)_q$-aryl] where q is an integer of from 1-3 and the aryl may optionally be substituted by 1 or 2 substituents Y, where each Y is as defined in claim 1;

(viii) -[$(CH_2)_r$-heteroaryl] where r is an integer of from 1-3, the heteroaryl having from 5 to 10 atoms and the heteroatoms(s) being selected from any of S, N, and O, and wherein the heteroatom(s) may optionally and independently be substituted by 1 or 2 substituents Y, where each Y is as defined in claim 1;

(ix) -[$(CH_2)_q$-aryl-O-$(CH_2)_r$-aryl] where q and r is each and independently an integer of from 1-3;

(x) -$(CH_2)_q$-[C_3-C_6 cycloalkyl] where q is from 1-2, optionally substituted by 1 or 2 substituents Y and wherein Y is as defined in claim 1;

R^2 is selected from any of

(i) hydrogen;

(ii) a straight or branched C_1-C_6 alkyl or C_2-C_6 alkenyl, where each alkyl and alkenyl may optionally be substituted by one or more aromatic or heteroaromatic substituents;

(iii) C_6 - C_{10} arylalkyl, wherein the aryl may optionally be substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom being selected from any of S,

N and O; and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined in claim 1;

(iv) heteoaryl-(C_5 - C_{10} alkyl), where the heteroaryl has from 5 to 10 atoms and the heteroatom being selected from any of S, N and O, and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined in claim 1;

(v) C_3-C_{10} cycloalkyl, optionally comprising one or more unsaturations and optionally susbtituted by one or more heteroaryl(s) where the heteroaryl has from 5 to 10 atoms and the heteroatom being selected from any of S, N and O;
and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined in claim 1;

(vi) C_6-C_{10} aryl, optionally and independently substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom(s) being selected from any of S, N and O and wherein the heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined in claim 1;

(vii) heteroaryl having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined in claim 1;

R^3 is selected from anyone of

(i) hydrogen;

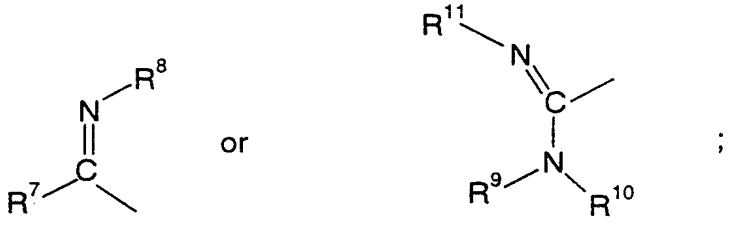
(ii) a straight or branched C_1-C_6 alkyl or C_2-C_6 alkenyl, where each alkyl and alkenyl may optionally be substituted by one or more aromatic or heteroaromatic substituents;

(iii) C_6 - C_{10} arylalkyl, wherein the aryl may optionally be substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined in claim 1;

(iv) heteoaryl-(C_5 - C_{10} alkyl), where the heteroaryl has from 5 to 10 atoms and the heteroatom being selected from any of S, N and O, and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined in claim 1;

(v) C_3-C_6 cycloalkyl, optionally comprising one or more unsaturations and optionally substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O, and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined in claim 1;

(vi)



;

wherein

R^7, R^8, R^9, R^{10} and R^{11} is each and independently selected from

(a) hydrogen;

(b) a straight or branched C_1-C_6 alkyl or C_2-C_6 alkenyl, where each alkyl and alkenyl may optionally be substituted by one or more aromatic or heteroaromatic substituents;

(c) C_6 - C_{10} arylalkyl, wherein the aryl may optionally be substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined in claim 1;

(d) heteoaryl-(C_5 - C_{10} alkyl), where the heteroaryl has from 5 to 10 atoms and the heteroatom being selected from any of S, N and O, and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined in claim 1;

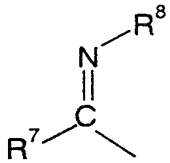
(e) C_3-C_{10} cycloalkyl, optionally comprising one or more unsaturations and optionally susbtituted by one or more heteroaryl(s) where the heteroaryl has from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined in claim 1;

(f) C_6-C_{10} aryl, optionally and independently substituted by one or more heteroaryl(s) having from 5 to 10 atoms and the heteroatom(s) being selected from any of S, N and O and wherein the heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined in claim 1.

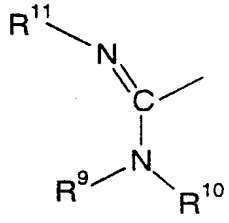
3. A compound according to claim 2, wherein

R^2 is hydrogen;

R^3 is



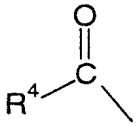
or



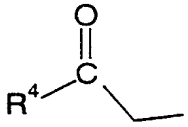
wherein R^7, R^8, R^9, R^{10} and R^{11} are as defined in claim 2.

m and n are each and independently 1 or 2;

Q is



or



wherein

R^4 is selected from

(i) phenyl;

(ii) heteroaryl having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; wherein the phenyl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents **Y** wherein each Y is as defined in claim 1;

(iii) cyclohexyl;

(iv) C_1-C_6 alkyl;

(v) C_1-C_3 alkoxy;

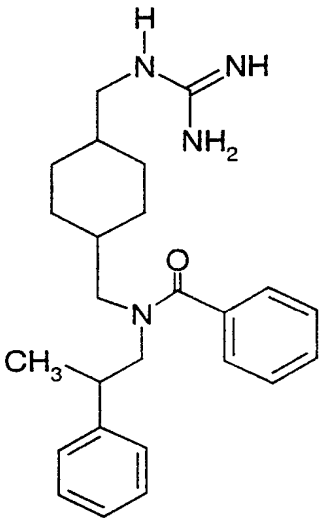
R^1 is

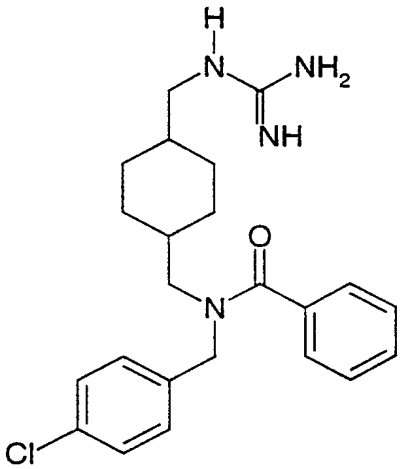
(i) -[$(CH_2)_q$-aryl] where q is an integer of from 1-3 and the aryl may optionally be substituted by 1 or 2 substituents Y, where each Y is as defined in claim 1; or

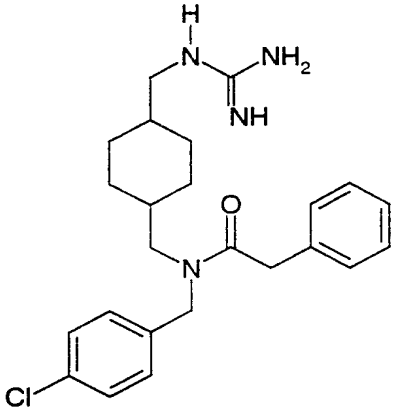
(ii) C_3-C_7 cycloalkyl, optionally comprising one or more unsaturations and optionally substituted by one or more of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, hydroxy; or substituted by one or more aryl(s), or heteroaryl(s) having from 5 to 10 atoms and the heteroatom(s) being selected from any of S, N and O and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined in claim 1;

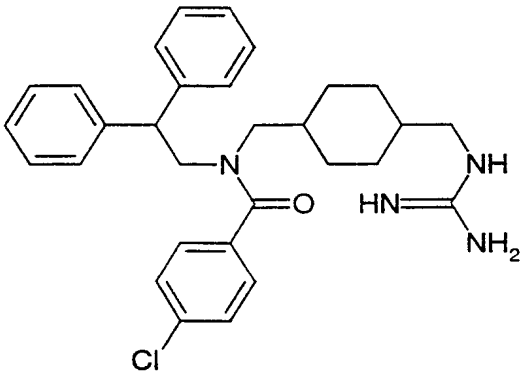
(iii) -(CH_2)-cyclohexyl;

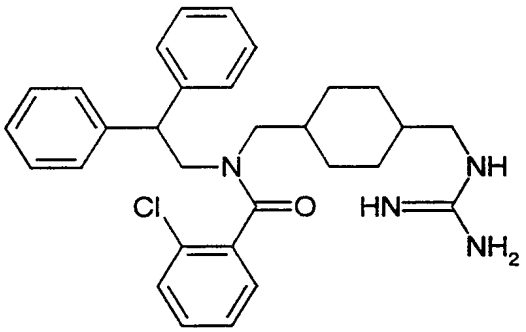
4. A compound according to claim 1, which compound is anyone selected from

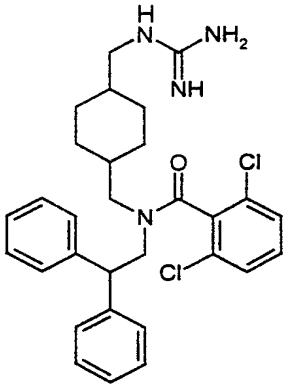


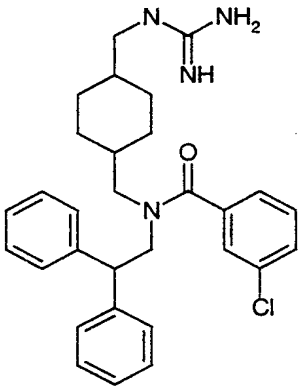


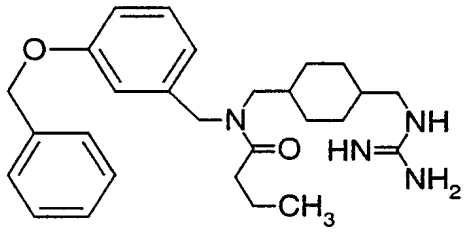


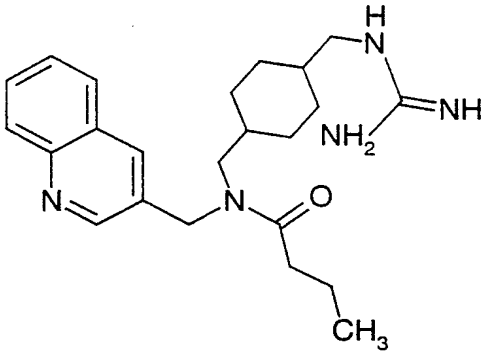


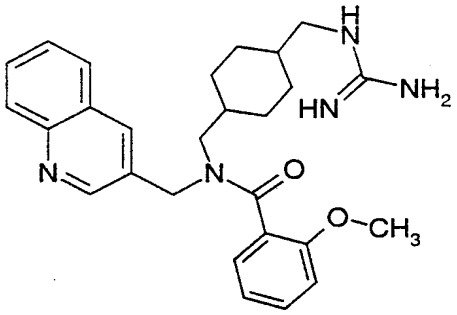


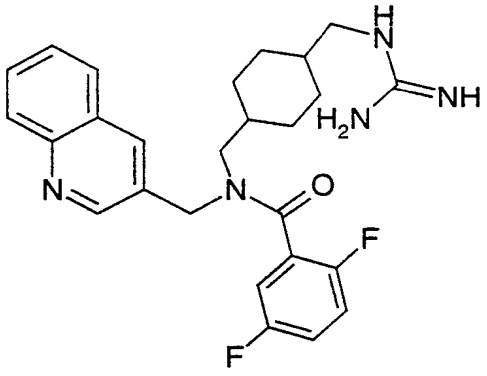


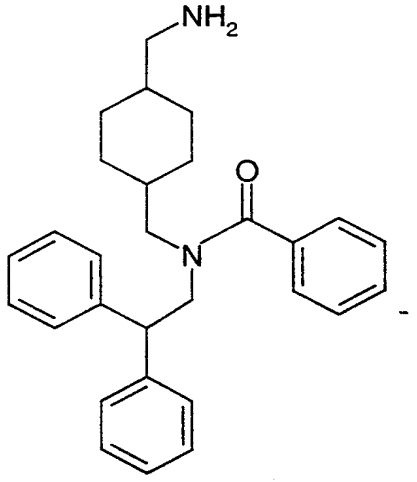




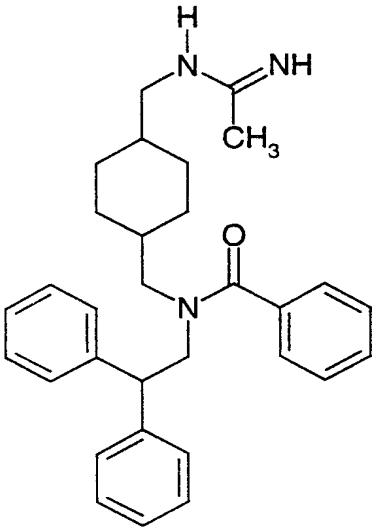


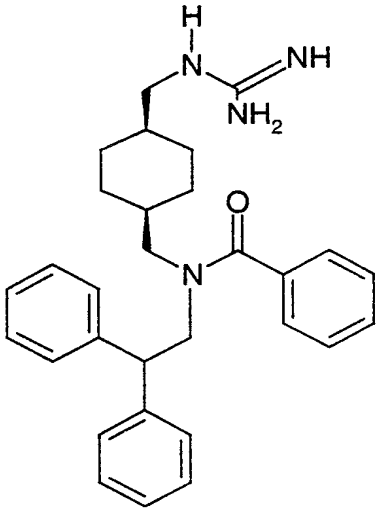


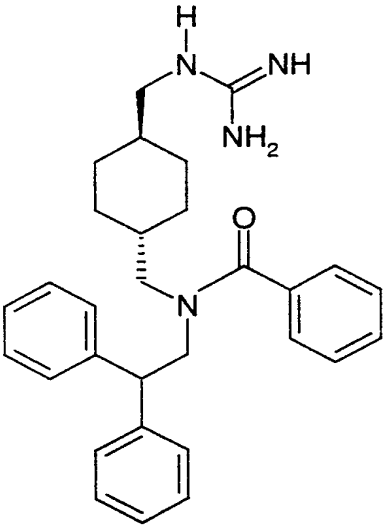


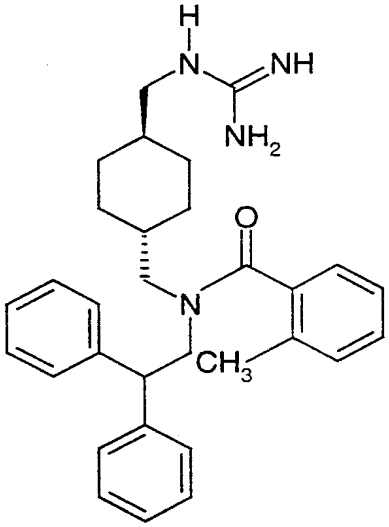


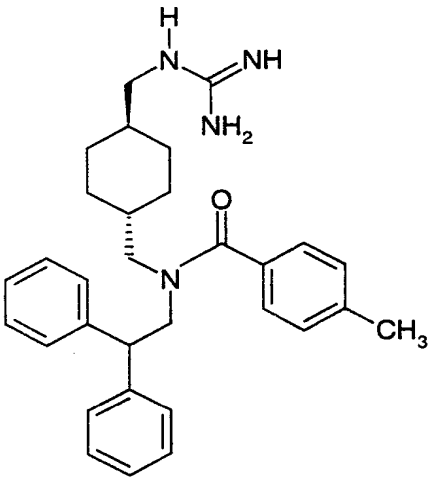
5

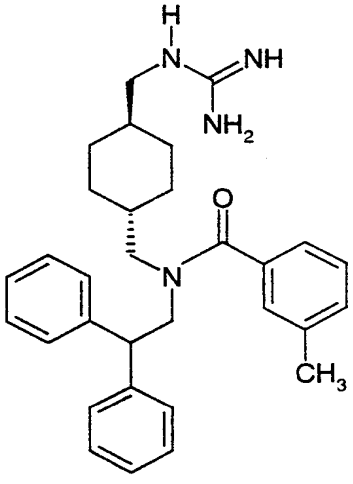


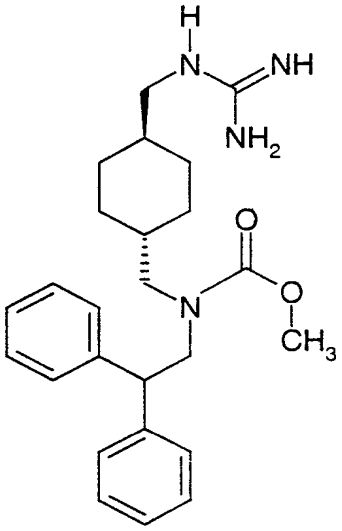


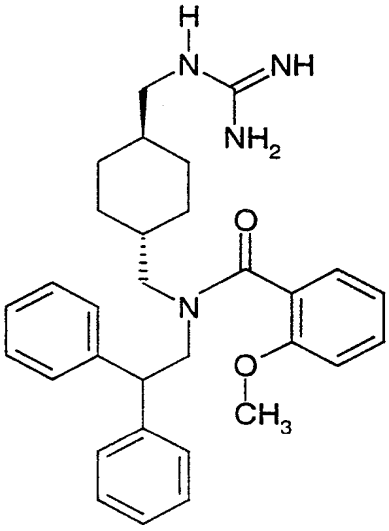


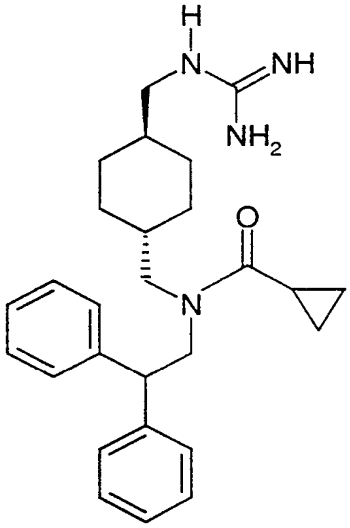


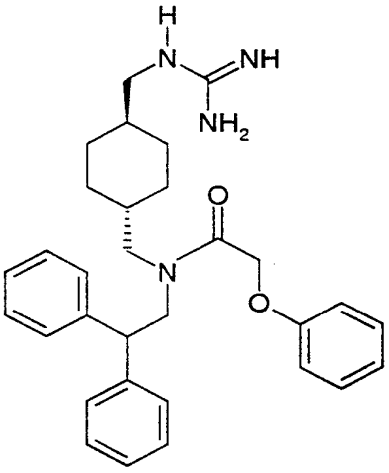




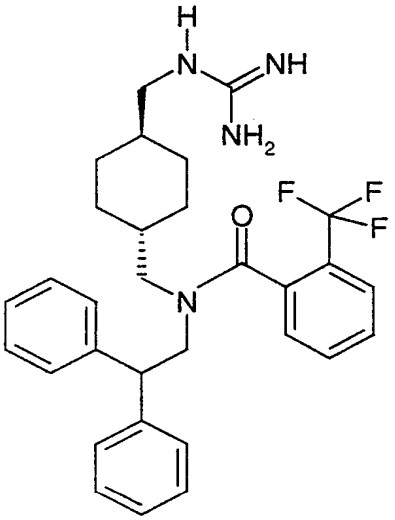


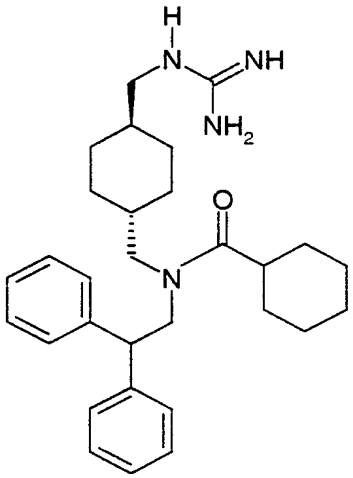


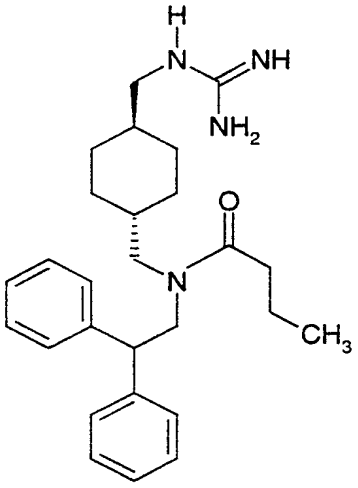


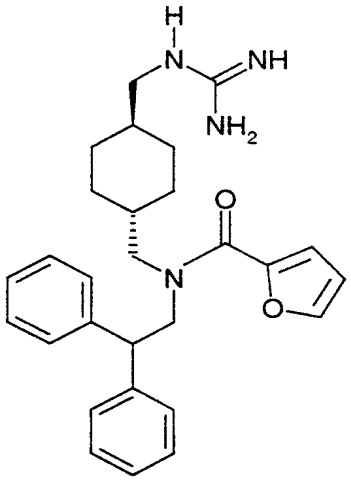


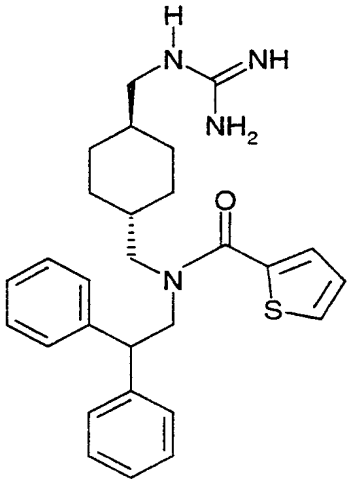
5

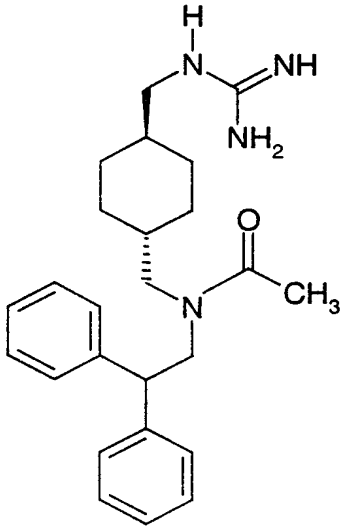


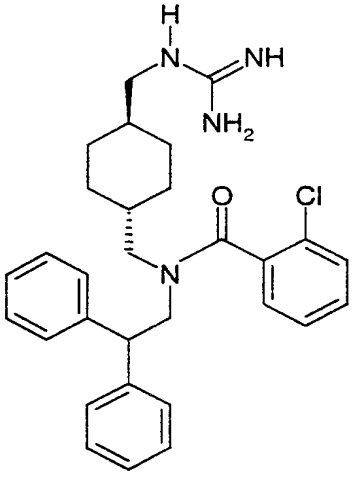


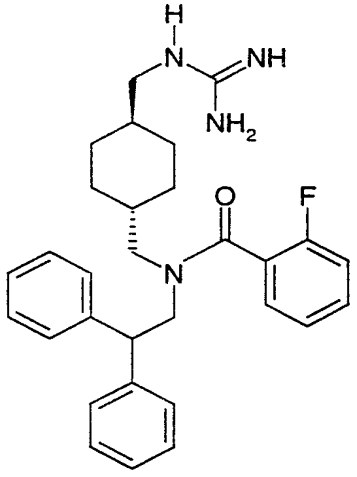


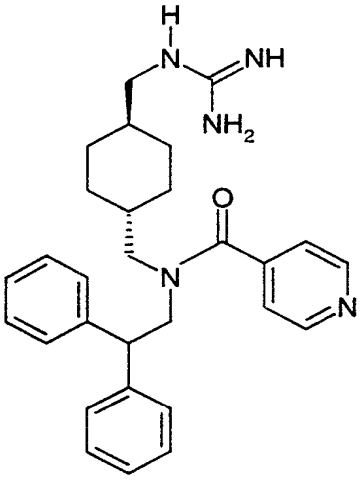


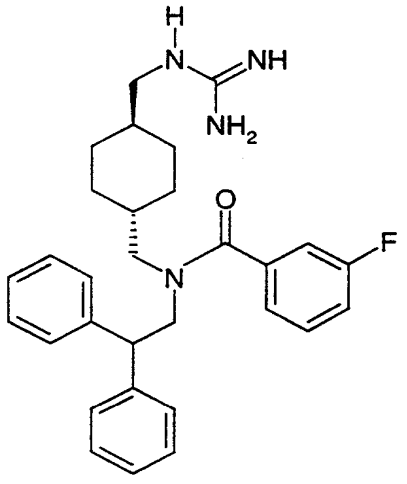


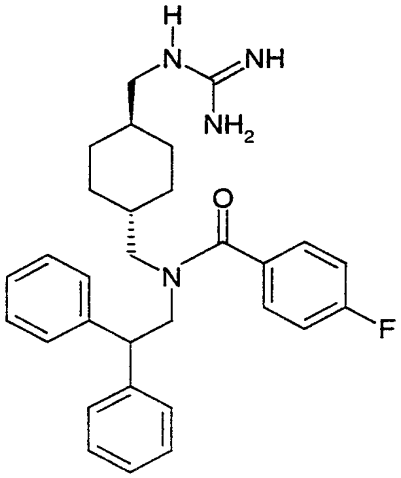


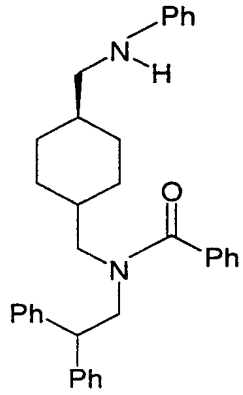


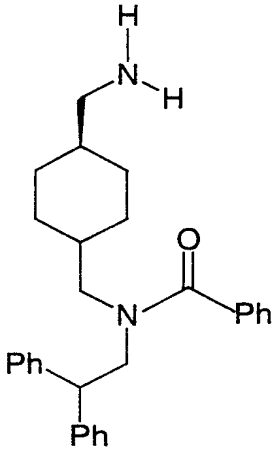


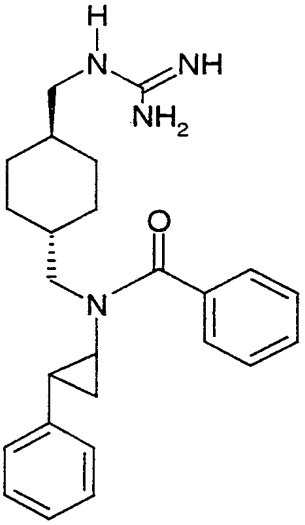


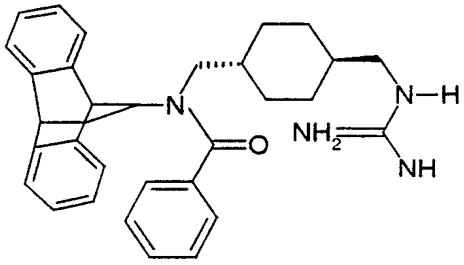


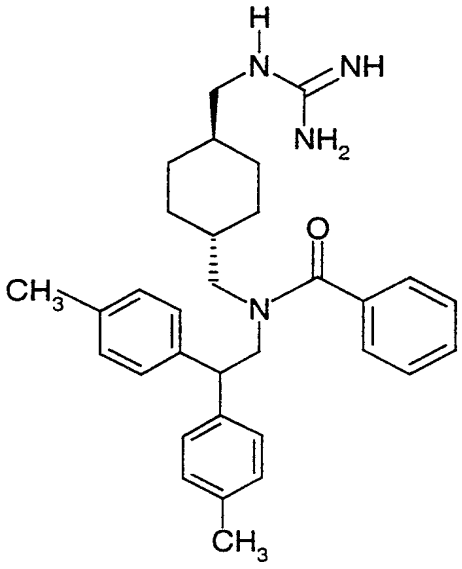


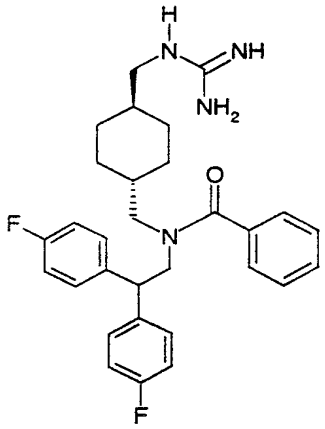


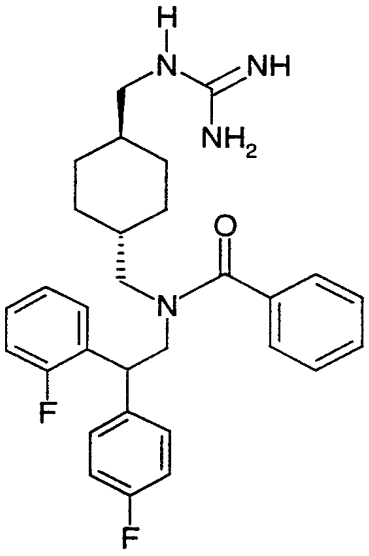


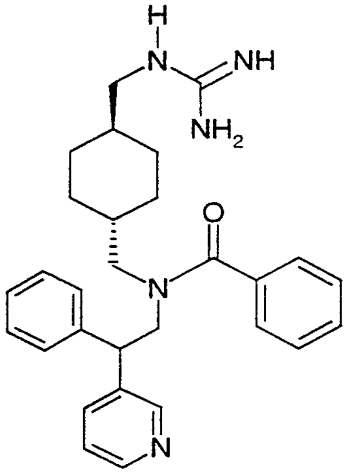


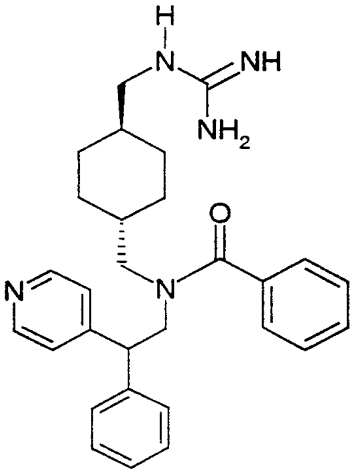


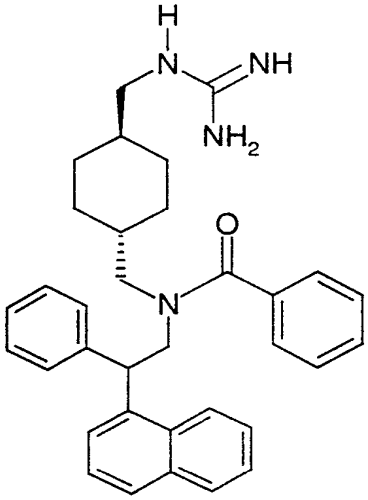


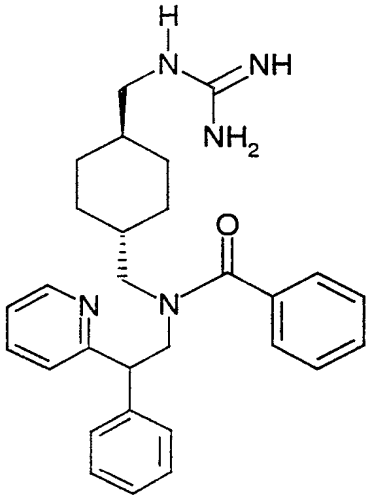


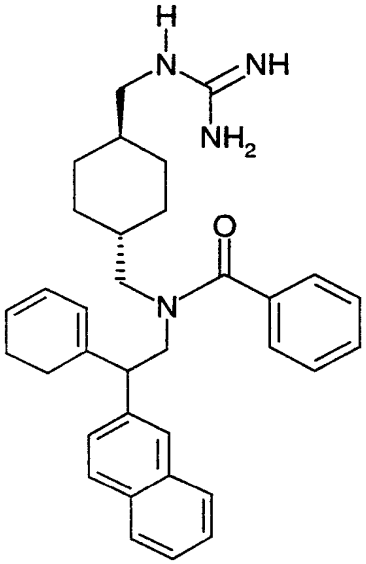


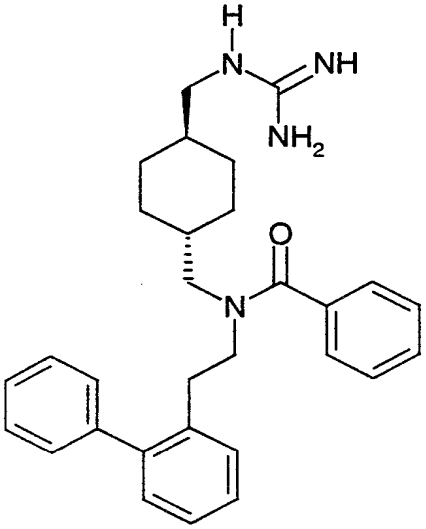


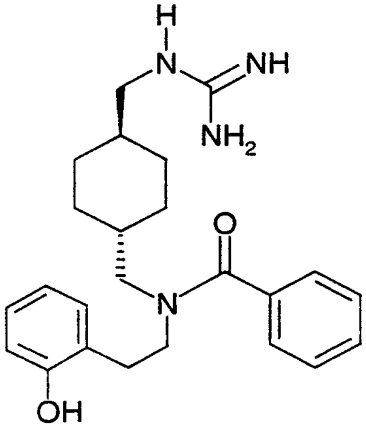


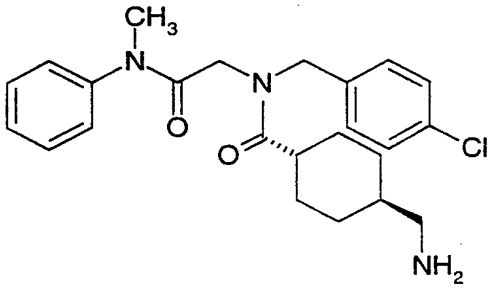


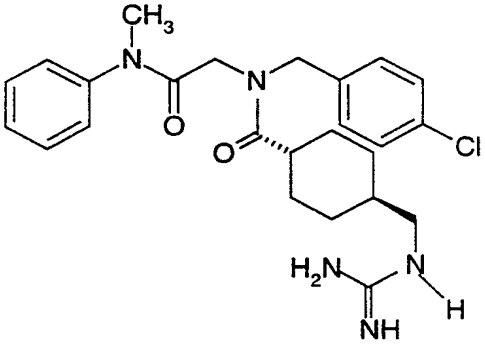


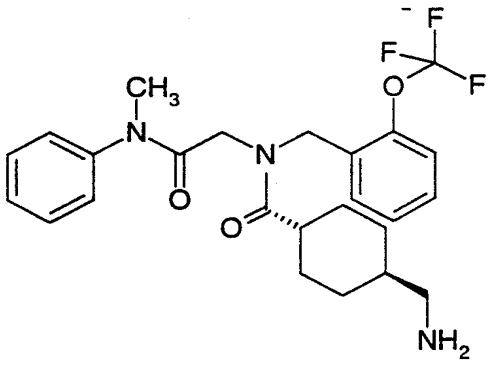


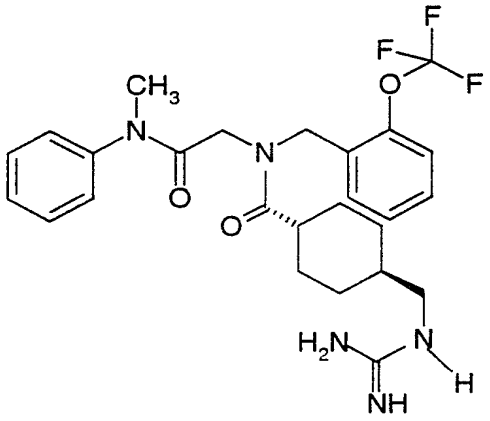


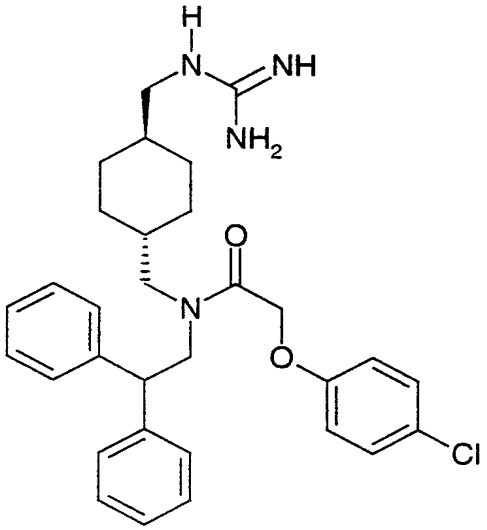




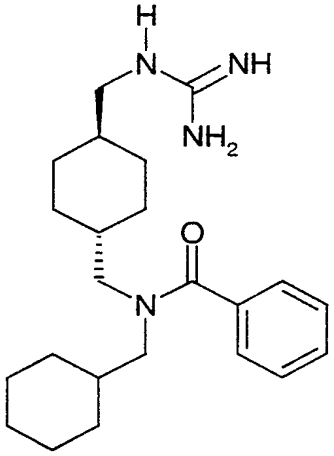




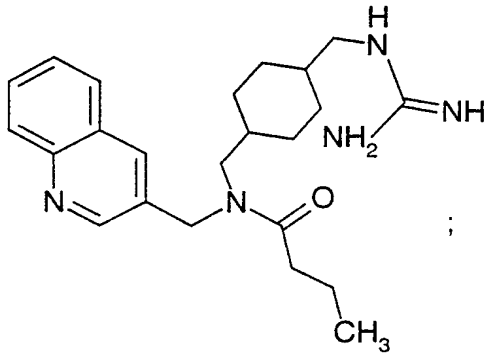




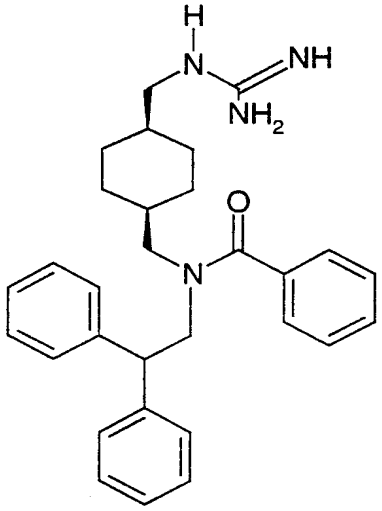
and



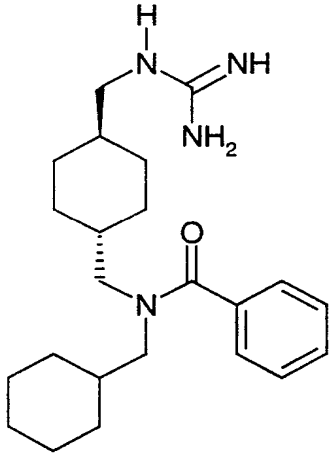
5. A compound according to claim 4, which compound is anyone selected from



;



; and



6. A compound according to any of the preceding claims, in form of its hydrochloride, sulfate, tartrate or citrate salts.

7. A compound according to any of claims 1-6 for use in therapy.

8. A compound according to claim 7, wherein the therapy is pain management.

9. A compound according to claim 7, wherein the therapy is directed towards gastrointestinal disorders.

10. A compound according to claim 7, wherein the therapy is directed towards spinal injuries.

11. A compound according to claim 7, wherein the therapy is directed to disorders of the sympathetic nervous system.

12. Use of a compound according to formula I of claim 1 for the manufacture of a medicament for use in the treatment of pain.

13. Use of a compound according to formula I of claim 1 for the manufacture of a medicament for use in the treatment of gastrointestinal disorders.

14. Use of a compound according to formula I of claim 1 for the manufacture of a medicament for use in the treatment of spinal injuries.

15. A compound according to any of claims 1-11, further characterised in that it is isotopically labelled.

16. Use of a compound according to claim 15 as a diagnostic agent.

17. An isotopically labelled compound of the formula I of claim 1.

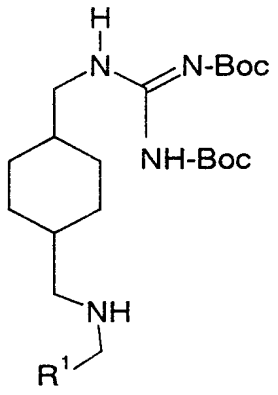
18. A diagnostic agent comprising a compound of the formula I of claim 1.

19. A pharmaceutical composition comprising a compound of the formula I according to claim 1 as an active ingredient, together with a pharmacologically and pharmaceutically acceptable carrier.

20. A process for the preparation of a compound of the formula I according to claim 1, whereby

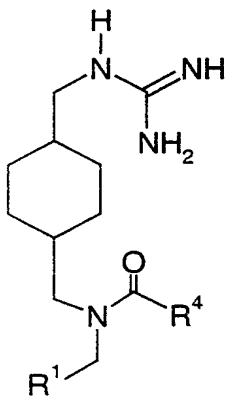
A)

(i) a cis/trans-mixture of 1,4-bis-aminomethyl cyclohexane is converted into a mono-(diBoc)guanidinomethyl derivative, which in turn is reacted with an aldehyde of the formula R^1CHO, providing a secondary amine of the formula (III)



(III)

(ii) the compound of the formula (III) is reacted with an acylating reagent of the formula R^4COCl and thereafter deprotected, providing a cis/trans-guanidinomethyl cyclohexane compound of the formula (VI)

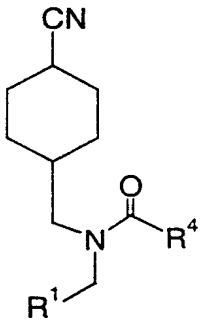


(VI)

; *or*

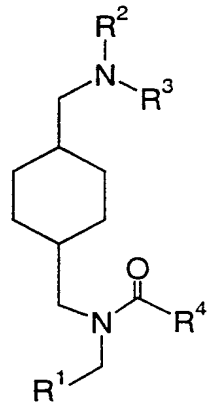
B)

(i) cis,trans-4-(aminomethyl)-cyclohexane carbonitrile is reacted with an aldehyde of the formula R^1CHO, which thereafter is reacted with an acylating reagent R^4COCl, providing a compound of the formula (VIII)



(VIII)

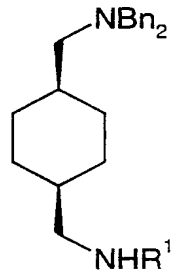
(ii) the nitrile group of the compound of the formula (VIII) is reduced and thereafter guanylated, amidinated or alkylated, providing a compound of the formula (X)



(X)

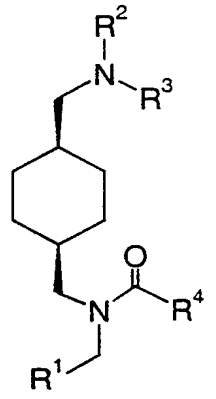
; *or*

C) cis-1,4-cyclohexane dicarboxylic acid anhydride is converted to the cis-acid amide, which thereafter is reacted with a primary amine, wherafter the carbonyl groups are reduced, providing a compound of formula (XIII)



(XIII)

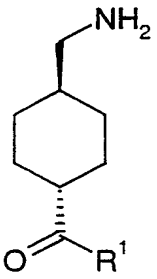
which in turn is acylated, reduced, and finally amidinated, alkylated or guanylated, providing a cis-compound of the formula (XVI)



(XVI)

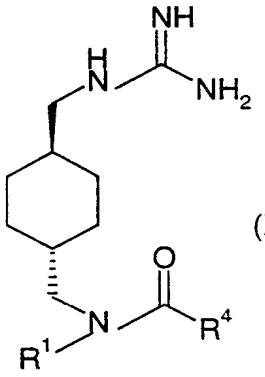
; *or*

D) trans-4-aminomethyl cyclohexane is protected, thereafter amidated and deprotected, providing a compound of the formula (XVIII)



(XVIII)

which in turn is reduced, protected, acylated, and finally deprotected, providing a compound of the formula (XXII)

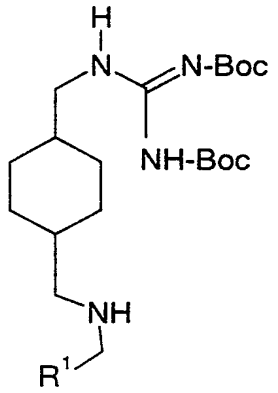


(XXII)

wherein

R^1, R^2, R^3 and R^4 in each step are as defined for formula I of claim 1.

21. A compound of the formula (III)



(III)

wherein

R^1 is selected from anyone of

(i) a straight or branched C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, where each alkyl, alkenyl or alkynyl may optionally be substituted by one or more aromatic or heteroaromatic substituents;

(ii) C_3-C_7 cycloalkyl, optionally comprising one or more unsaturations and optionally substituted by one or more of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, hydroxy; or substituted by one or more aryl(s), or heteroaryl(s) having from 5 to 10 atoms and the heteroatom(s) being selected from any of S, N and O and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined in claim 1;

(iii) halogen or C_1-C_6 alkoxy;

(iv) C_6-C_{10} aryl;

(v) heteroaryl having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined in claim 1;

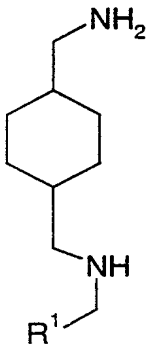
(vi) 9,10-dihydro-9,10-ethanoantracenyl;

(vii) -[$(CH_2)_q$-aryl] where q is an integer of from 1-3 and the aryl may optionally be substituted by 1 or 2 substituents Y, where each Y is as defined in claim 1;

(viii) -[$(CH_2)_r$-heteroaryl] where r is an integer of from 1-3, the heteroaryl having from 5 to 10 atoms and the heteroatoms(s) being selected from any of S, N, and O, and wherein the heteroatom(s) may optionally and independently be substituted by 1 or 2 substituents Y, where each Y is as defined in claim 1;

(ix) -[$(CH_2)_q$-aryl-O-$(CH_2)_r$-aryl] where q and r is each and independently an integer of from 1-3.

22. A compound of the formula (VII)



(VII)

wherein

R^1 is selected from anyone of

(i) a straight or branched C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, where each alkyl, alkenyl or alkynyl may optionally be substituted by one or more aromatic or heteroaromatic substituents;

(ii) C_3-C_7 cycloalkyl, optionally comprising one or more unsaturations and optionally substituted by one or more of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, hydroxy; or substituted by one or more aryl(s), or heteroaryl(s) having from 5 to 10 atoms and the heteroatom(s) being selected from any of S, N and O and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined in claim 1;

(iii) hydrogen, halogen or C_1-C_6 alkoxy;

(iv) C_6-C_{10} aryl;

(v) heteroaryl having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined in claim 1;

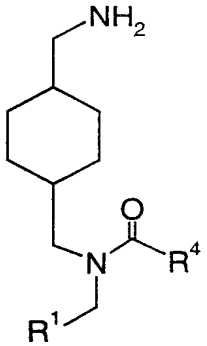
(vi) 9,10-dihydro-9,10-ethanoantracenyl;

(vii) -[$(CH_2)_q$-aryl] where q ia an integer of from 1-3 and the aryl may optionally be substituted by 1 or 2 substituents Y, where each Y is as defined in claim 1;

(viii) -[$(CH_2)_r$-heteroaryl] where r is an integer of from 1-3, the heteroaryl having from 5 to 10 atoms and the heteroatoms(s) being selected from any of S, N, and O, and wherein the heteroatom(s) may optionally and independently be substituted by 1 or 2 substituents Y, where each Y is as defined in claim 1;

(ix) -[$(CH_2)_q$-aryl-O-$(CH_2)_r$-aryl] where q and r is each and independently an integer of from 1-3.

23. A compound of the formula (IX)



(IX)

wherein

R^1 is selected from anyone of

(i) a straight or branched C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, where each alkyl, alkenyl or alkynyl may optionally be substituted by one or more aromatic or heteroaromatic substituents;

(ii) C_3-C_7 cycloalkyl, optionally comprising one or more unsaturations and optionally substituted by one or more of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, hydroxy; or substituted by one or more aryl(s), or heteroaryl(s) having from 5 to 10 atoms and the heteroatom(s) being selected from any of S, N and O and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined in claim 1;

(iii) hydrogen, halogen or C_1-C_6 alkoxy;

(iv) C_6-C_{10} aryl;

(v) heteroaryl having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined in claim 1;

(vi) 9,10-dihydro-9,10-ethanoantracenyl;

(vii) -[$(CH_2)_q$-aryl] where q ia an integer of from 1-3 and the aryl may optionally be substituted by 1 or 2 substituents Y, where each Y is as defined in claim 1;

(viii) -[$(CH_2)_r$-heteroaryl] where r is an integer of from 1-3, the heteroaryl having from 5 to 10 atoms and the heteroatoms(s) being selected from any of S, N, and O, and wherein the heteroatom(s) may optionally and independently be substituted by 1 or 2 substituents Y, where each Y is as defined in claim 1;

(ix) -[$(CH_2)_q$-aryl-O-$(CH_2)_r$-aryl] where q and r is each and independently an integer of from 1-3; and

R^4 is selected from anyone of

(i) C_6-C_{10} aryl; or

(ii) heteroaryl having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined in claim 1;

(iii) hydrogen;

(iv) a straight or branched C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl;

(v) C_1-C_3 alkoxy;

(vi) saturated or unsaturated C_3 - C_{10} cycloalkyl, optionally and independently

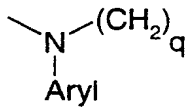
substituted by one or more aryl(s) or heteroaryl(s) having from 5 to 10 atoms and the heteroatom(s) being selected from any of S, N and O and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined in claim 1;

(vii) -[$(CH_2)_q$-aryl] where q is an integer of from 1-3, and the aryl may optionally be substituted by 1 or 2 substituents Y, where each Y is as defined in claim 1;

(viii) -[$(CH_2)_r$-heteroaryl] where r is an integer of from 1-3, the heteroaryl having from 5 to 10 atoms and the heteroatoms(s) being selected from any of S, N, and O, and wherein the heteroatom(s) may optionally and independently be substituted by 1 or 2 substituents Y, where each Y is as defined in claim 1;

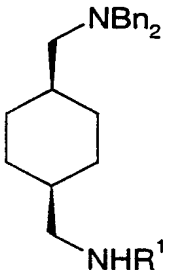
(ix) -[CH_2-O-aryl] where the aryl may optionally be substituted by 1 or 2 substituents Y, where each Y is as defined in claim 1;

(x)



where q is an integer of from 1-3, and the aryl may optionally be substituted by 1 or 2 substituents Y, where each Y is as defined in claim 1.

24. A compound according to formula (XIII)



(XIII)

wherein

R^1 is selected from anyone of

(i) a straight or branched C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, where each alkyl, alkenyl or alkynyl may optionally be substituted by one or more aromatic or heteroaromatic substituents;

(ii) C_3-C_7 cycloalkyl, optionally comprising one or more unsaturations and optionally substituted by one or more of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, hydroxy; or substituted by one or more aryl(s), or heteroaryl(s) having from 5 to 10 atoms and the heteroatom(s) being selected from any of S, N and O and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined in claim 1;

(iii) hydrogen, halogen or C_1-C_6 alkoxy;

(iv) C_6-C_{10} aryl;

(v) heteroaryl having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined in claim 1;

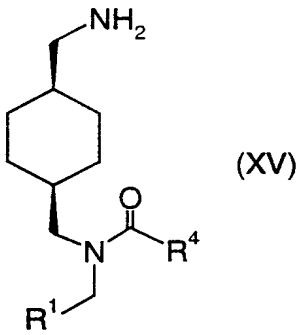
(vi) 9,10-dihydro-9,10-ethanoantracenyl;

(vii) -[$(CH_2)_q$-aryl] where q ia an integer of from 1-3 and the aryl may optionally be substituted by 1 or 2 substituents Y, where each Y is as defined in claim 1;

(viii) -[$(CH_2)_r$-heteroaryl] where r is an integer of from 1-3, the heteroaryl having from 5 to 10 atoms and the heteroatoms(s) being selected from any of S, N, and O, and wherein the heteroatom(s) may optionally and independently be substituted by 1 or 2 substituents Y, where each Y is as defined in claim 1;

(ix) -[$(CH_2)_q$-aryl-O-$(CH_2)_r$-aryl] where q and r is each and independently an integer of from 1-3.

25. A compound according to formula (XV)



(XV)

wherein

R^1 is selected from anyone of

(i) a straight or branched C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, where each alkyl, alkenyl or alkynyl may optionally be substituted by one or more aromatic or heteroaromatic substituents;

(ii) C_3-C_7 cycloalkyl, optionally comprising one or more unsaturations and optionally substituted by one or more of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, hydroxy; or substituted by one or more aryl(s), or heteroaryl(s) having from 5 to 10 atoms and the heteroatom(s) being selected from any of S, N and O and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined in claim 1;

(iii) hydrogen, halogen or C_1-C_6 alkoxy;

(iv) C_6-C_{10} aryl;

(v) heteroaryl having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined inclaim 1;

(vi) 9,10-dihydro-9,10-ethanoantracenyl;

(vii) -[$(CH_2)_q$-aryl] where q ia an integer of from 1-3 and the aryl may optionally be substituted by 1 or 2 substituents Y, where each Y is as defined in claim 1;

(viii) -[$(CH_2)_r$-heteroaryl] where r is an integer of from 1-3, the heteroaryl having from 5 to 10 atoms and the heteroatoms(s) being selected from any of S, N, and O, and wherein the heteroatom(s) may optionally and independently be substituted by 1 or 2 substituents Y, where each Y is as defined in claim 1;

(ix) -[$(CH_2)_q$-aryl-O-$(CH_2)_r$-aryl] where q and r is each and independently an integer of from 1-3; and

R^4 is selected from anyone of

(i) C_6-C_{10} aryl; or

(ii) heteroaryl having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y where each Y is as defined in claim 1;

(iii) hydrogen;

(iv) a straight or branched C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl;

(v) C_1-C_3 alkoxy;

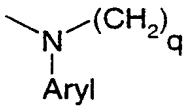
(vi) saturated or unsaturated C_3 - C_{10} cycloalkyl, optionally and independently substituted by one or more aryl(s) or heteroaryl(s) having from 5 to 10 atoms and the heteroatom(s) being selected from any of S, N and O and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined in claim 1;

(vii) -[$(CH_2)_q$-aryl] where q is an integer of from 1-3, and the aryl may optionally be substituted by 1 or 2 substituents Y, where each Y is as defined in claim 1;

(viii) -[$(CH_2)_r$-heteroaryl] where r is an integer of from 1-3, the heteroaryl having from 5 to 10 atoms and the heteroatoms(s) being selected from any of S, N, and O, and wherein the heteroatom(s) may optionally and independently be substituted by 1 or 2 substituents Y, where each Y is as defined in claim 1;

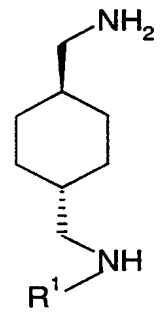
(ix) -[CH_2-O-aryl] where the aryl may optionally be substituted by 1 or 2 substituents Y, where each Y is as defined in claim 1;

(x)



where q is an integer of from 1-3, and the aryl may optionally be substituted by 1 or 2 substituents Y, where each Y is as defined in claim 1.

26. A compound of the formula (XIX)



(XIX)

wherein

R^1 is selected from anyone of

(i) a straight or branched C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, where each alkyl, alkenyl or alkynyl may optionally be substituted by one or more aromatic or heteroaromatic substituents;

(ii) C_3-C_7 cycloalkyl, optionally comprising one or more unsaturations and optionally substituted by one or more of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, hydroxy; or substituted by one or more aryl(s), or heteroaryl(s) having from 5 to 10 atoms and the heteroatom(s) being selected from any of S, N and O and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined in claim 1;

(iii) hydrogen, halogen or C_1-C_6 alkoxy;

(iv) C_6-C_{10} aryl;

(v) heteroaryl having from 5 to 10 atoms and the heteroatom being selected from any of S, N and O; wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y wherein each Y is as defined in claim 1;

(vi) 9,10-dihydro-9,10-ethanoantracenyl;

(vii) -[$(CH_2)_q$-aryl] where q ia an integer of from 1-3 and the aryl may optionally

be substituted by 1 or 2 substituents Y, where each Y is as defined in claim 1;

(viii) -[$(CH_2)_r$-heteroaryl] where r is an integer of from 1-3, the heteroaryl having from 5 to 10 atoms and the heteroatoms(s) being selected from any of S, N, and O, and wherein the heteroatom(s) may optionally and independently be substituted by 1 or 2 substituents Y, where each Y is as defined in claim 1;

(ix) -[$(CH_2)_q$-aryl-O-$(CH_2)_r$-aryl] where q and r is each and independently an integer of from 1-3.

27. A method for the treatment of pain, whereby an effective amount of a compound of the formula I according to claim 1 is administered to a subject in need of pain management.

28. A method for the treatment of gastrointestinal disorders, whereby an effective amount of a compound of the formula I according to claim 1, is administered to a subject suffering from said gastrointestinal disorder.

29. A method for the treatment of spinal injuries, whereby an effective amount of a compound of the formula I according to claim 1, is administered to a subject suffering from said spinal injury.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/01074

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07C 279/12, C07C 233/78, C07C 237/24, C07D 215/12, C07D 307/46, C07D 333/26, C07D 213/54, C07D 213/24, A61K 51/00, 49/00, 31/155, 31/165, 31/33
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07C, C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4762949 A (KENNETH L. RINEHART, JR. ET AL), 9 August 1988 (09.08.88), the claims	1,6-11,15, 17-20
	--	
X	WO 9807420 A1 (AGOURON ACQUISITION CORP.), 26 February 1998 (26.02.98), page 47, line 1 - line 10; page 52	21
A		1-20,22-29
	--	
A	WO 9719913 A1 (DR. KARL THOMAE GMBH), 5 June 1997 (05.06.97)	1-29
	--	

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 Sept 1999	16 -10- 1999
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Gerd Strandell/EÖ Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/01074

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	STN International, File CAPLUS, CAPLUS accession no. 1976:58997, Document no. 84:58997, Daiichi Seiyaku Co., Ltd.: "Bisquanidino compounds"; JP,A2,50111029, 19750901 -- --------	1-29

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/01074

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 16, 27-29
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/01074

Claims 16, 27-29 relate to methods of treatment of the human or animal body by surgery or by therapy. See PCT, Rule 39.1 (iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

30/08/99

International application No.
PCT/SE 99/01074

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4762949 A	09/08/88	NONE	
WO 9807420 A1	26/02/98	AU 4159297 A	06/03/98
WO 9719913 A1	05/06/97	CA 2235937 A	05/06/97
		DE 19544685 A	05/06/97
		EP 0865425 A	23/09/98